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ANNALS OF
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THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN*

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THE results of treatment of subacute bacterial endocarditis have been as disappointing and unavailing as of any disease known to medicine. The disease is not uncommon and is found most frequently in localities where rheumatic heart disease is common. Until the present time treatment has been discouraging; attempts to immunize the patient by vaccines, serums, and non-specific shock therapies were very disappointing; in fact these methods seemed to shorten the patient's life rather than prolong it. Intravenous injections of mercurochrome, acriflavine, and gentian violet produced no results, although some of them were encouraging, particularly the use of merthiolate which seemed to cure a similar disease produced experimentally in animals but proved to be of no value in treating human beings.

The advent of the sulfa drugs raised high hopes that at last a remedy had been found which would cure this dread disease. However, sulfanilamide early proved disappointing and other sulfa compounds were tried; then sulfa drugs in combination with other therapeutic measures, such as fever therapy, heparin, and typhoid vaccines. It was then that reports began to appear concerning patients who had recovered from subacute bacterial endocarditis through medical treatment. The advent of penicillin once more raised our hopes but mindful of the disappointments shown by the sulfa compounds we were skeptical of reported cures of subacute bacterial endocarditis by penicillin.

We wish to report six cases of subacute bacterial endocarditis treated with penicillin, in three of which the progress made by the patient has been such that a claim of cure seems justified. It is probable that more cases will be reported as cured by penicillin since the supply of this drug has been greatly increased. It is also probable that most patients will have had an

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abortive attempt at cure with some of the sulfa drugs before receiving penicillin. Consequently it is only fair to evaluate the percentage of individuals who may be expected to recover from this disease spontaneously or from the use of other chemotherapeutic agents. In a series of 1,500 cases of subacute bacterial endocarditis Libman [1] reported only 22 spontaneous recoveries. Small as this number of cures is, it is far greater than the three spontaneous recoveries among 1,096 cases collected by Lichtman.[2] Combining these two figures gives a total of 25 spontaneous recoveries among nearly 2,600 cases, or less than 1 per cent. The results of treating subacute bacterial endocarditis by chemotherapy (sulfonamides) offer some improvement over the above figure. Lichtman collected 489 cases to which may be added some reported more recently by Galbreath and Hull [3] and also a few reported by Bunn,[4] which brings the total up to 535. Twenty-four of this number were reported cured, thus giving a total of 4.5 per cent of cases cured by sulfonamides alone and not in combination with other therapeutic measures. The use of sulfonamides in combination with heparin was advocated in the hope that the heparin would prevent the formation of fibrin clots on the valve leaflets and so eliminate the bacterial-laden vegetation from the valves. Of 109 cases reported treated by the combination of heparin and sulfonamides seven recovered, thus showing a total of 6.5 per cent cured. Krusen [5] and others reported that the blood stream can be sterilized by use of hyperpyrexia alone, even though it cannot be kept sterile. The fact that positive cultures from the blood stream can be made within a few days after sterilization of the blood by hyperpyrexia is probably due to the breaking off of infected vegetations from the valves and reinfection of the blood stream. Chemotherapy, in combination with hyperpyrexia induced by the fever cabinet or the Kettering hypertherm, in 61 cases yielded only four cures, or a total of 6.5 per cent. This is almost the same percentage as by chemotherapy alone. Solomon [6] reported 22 cases treated by chemotherapy plus the use of intravenous typhoid vaccine with five cures from *Streptococcus viridans* infection, but 23 other cases reported by Lichtman resulted in only two additional cures. These reports give this form of therapy an average of 15 per cent in the 45 cases reported. Just how much the percentage of cures will increase through the use of penicillin is difficult to determine at this time. It is hoped that the percentage will mount considerably. Herrell, Nichols and Heilman,[7] at the Mayo Clinic, reported that four cases of subacute bacterial endocarditis they had treated with penicillin resulted in failure. However, they used penicillin in very small amounts and what the outcome would have been if they had used larger doses is conjecturable. Evans [8] treated four cases with a cure in one. He found that very large doses were necessary and used four and one-half million units on the individual who recovered. This man is now well and working 10 months after his illness.

The first three cases presented here are frank failures. Two of these cases received less than 3 million units, which from our observation seems

insufficient to produce a lasting cure. On the other hand two of these three were advanced in age; the other, although young, was almost in extremis on admission to the hospital. Failure was expected in one case because the organism isolated from her blood was only slightly inhibited in vitro by penicillin.

Case Reports

Case 1. O. D., white female, age 68, was admitted to the hospital July 24, 1944, with the history of illness with fever and general malaise of eight weeks' duration. Five weeks previously she developed generalized aching, night sweats with some loss of weight, and also anorexia and nausea. Two weeks previous to admission she had diarrhea with blood and mucus in her stools. She developed shortness of breath at this time. One year previous to admission a doctor had told her she had a "leak" in her heart. Otherwise her cardio-respiratory history was negative.

Physical Examination. On admission her temperature was 100 3/5°, pulse 88, respirations 18, blood pressure 140 mm. Hg systolic and 74 mm. diastolic. She did not appear acutely ill. The general examination was essentially negative. Heart was enlarged and the rate was regular. She had a grade 3, fairly harsh systolic murmur at the apex and over the aortic area. The spleen was not palpable. No petechiae were observed.

Laboratory Reports. Red blood cells averaged about 4,200,000; hemoglobin about 11 grams; sedimentation rate varied from 117 mm. on admission to 107 mm. two weeks later; white blood cells varied from 9,000 to 11,000 and as low as 7,000. Five blood cultures were positive for alpha hemolytic streptococcus, or *Streptococcus viridans.* At 4 p.m. on August 2, her tenth hospital day, she was started on twenty-five thousand units of penicillin in 2 c.c. of saline intramuscularly every two hours.

Treatment. Before penicillin was started the temperature varied from 101° to 102° F., and after that it dropped to 99.5°. On the fourteenth hospital day the heart murmur was still the same and the temperature remained about 99° F. She was given 400 c.c. of whole blood. She received a total of 2,975,000 units of penicillin up until August 12, 1944. Her temperature remained about 99° with the exception of one day from the time the drug was started. She was dismissed from the hospital on August 19. On September 5 she reported that she was not well and was complaining that she ached all over and that her ankles were swelling. Failure in this case was expected because her organisms were only slightly inhibited by penicillin in vitro.

Case 2. J. H., colored male, age 72, was admitted to the hospital on May 16, 1944. He had been in good health until the first of April, 1944, at which time he began to have fever without chills, loss of weight, anorexia, and severe lassitude. His illness forced him to stay in bed for about one week before his admission. At this time he developed a severe precordial pain which was noted only on motion of the chest wall. This was described as a "catch-like" pain. There was no history of previous heart disease, syphilis, or rheumatic fever.

Physical Examination. The temperature on admission was 100° F. Pulse 90. Blood pressure 150 mm. Hg systolic and 100 mm. diastolic. He was an elderly colored man in no acute distress, but chronically ill. Eyes showed pale conjunctivae with petechiae in the lower left lid. The fundi showed no hemorrhages or exudates but there was one plus arteriosclerosis. The heart was enlarged to the left and there was a to and fro murmur heard over the aortic area. At the apex there was a soft diastolic murmur. The rate and rhythm were regular. The liver was palpable 3 cm. below the costal border. There was a right indirect inguinal hernia extending down into the right scrotum. Otherwise physical examination was negative.

Laboratory Reports. Red blood cell count was 3,800,000 with 10 grams of hemoglobin. Sedimentation rate 85 mm. White blood cells, 10,950, with 83 per cent polymorphonuclears. Blood culture on admission showed an alpha hemolytic streptococcus. Phenolsulfonphthalein test was within normal limits. Non-protein-nitrogen four days after admission was 32, with a total protein of 5.5 grams.

Roentgen-ray showed marked left ventricular enlargement with tortuosity of the thoracic aorta.

Hospitalization. Cultures of the blood were taken daily after admission, all of which grew alpha hemolytic streptococcus. This was continued until penicillin could be started on May 24. Twenty-five thousand units were given every three hours. On May 29 the cultures of the blood became negative. By this time the patient had already regained his strength and continued to feel subjectively well the remainder of his hospital stay. On June 6 the course of penicillin was completed and 2,800,000 units had been given. The cultures of the blood had remained negative up until June 5 but one done on June 8 was again positive and they remained positive until he left the hospital. On June 13 he was placed on full dosages of sulfadiazine. The blood cultures remained positive and the patient subjectively well. On June 17 he was discharged at his own insistence. When last seen his health and strength were failing rapidly.

Case 3. C. R., white, female, age 20, was admitted to the hospital on April 17, 1944. At that time she complained of heart and joint pains which began in November 1943 following an attack of influenza with malaise, chills and headache, and paralysis of the left side. In January 1944 she developed a polyarticular migrating pain at the left ankle, with swollen, hot, tender joints involving the ankle and then both knees, wrist, elbow. This cleared up with no residual damage. Two weeks before admission she had an attack of palpitation lasting five to ten minutes. Frequently in the past she had attacks of dyspnea which had been relieved by erect posture. History revealed that she had frequent epistaxis as a child, with sore throat. There is no other history of rheumatism or chorea.

Physical Examination. Temperature on admission 100.2° F.; pulse 120; respirations 40; blood pressure 110 mm. Hg systolic and 50 mm. diastolic. She was acutely ill, considerably undernourished, with evidence of recent weight loss. The left wrist, hand, fingers, elbow and ankle were swollen, tender, and very painful on motion. The eyes showed some petechiae in the right conjunctiva; fundi were negative. The throat was inflamed. Examination of the heart revealed a diffuse apex impulse with a systolic thrill at the apex and a loud harsh systolic murmur and a low-pitched diastolic murmur heard at the apex. The tip of the spleen could barely be felt. There was some clubbing of the fingers. Reflexes were all hyperactive. She was hyper-irritable and unstable emotionally, crying during the entire time the history was being taken.

Laboratory Reports. Her red blood cells were 3,900,000, with 12.4 grams of hemoglobin. Sedimentation rate was 115 mm. and ranged down to as low as 16 mm. an hour before her death. The red cell count did not change markedly. The white blood cell count on admission was 12,000, eighty per cent of which were polymorphonuclears; this ranged as high as 23,000 and as low as 9,300 before her death. Non-protein-nitrogen was 38 mg. one month after admission to the hospital and 92 mg. before death. Four consecutive blood cultures on admission revealed alpha hemolytic streptococcus. Roentgenogram of the chest taken shortly after admission revealed generalized cardiac enlargement, mitral configuration, and pulmonary congestion.

Hospitalization. The first five days in the hospital her temperature was spiking, going as high as 104° F. She was started on sulfadiazine on the fourth day and this was continued to the seventh hospital day. Penicillin was started in doses of 200,000

units per day on the eleventh hospital day and this was continued for 20 days. A total of 4.5 million units were used. The patient went into marked congestive failure during the treatment. She was digitalized and was given ammonium chloride, salyrgan, urea crystals, and vitamins, etc., with little relief. Both pleural cavities were tapped, and 1,000 to 2,000 c.c. of fluid were removed at various and irregular intervals. Her temperature came back to normal about five days after the discontinuance of penicillin and remained normal throughout the rest of her hospitalization. She became very irritable, would not eat and would not take any medication by mouth. Plasma and all other measures for diuresis and increasing the strength of the heart were unsuccessful. She gradually became weaker and died on the fifty-ninth hospital day.

Necropsy was obtained. The diagnoses were: (1) Rheumatic heart disease, with mitral insufficiency. (2) Subacute bacterial endocarditis, due to alpha hemolytic streptococci. (3) Old cerebral embolism.

The first case presents a fairly typical picture of an endocarditis superimposed upon valves of the heart that were already damaged. The failure of penicillin to inhibit organisms isolated from her blood stream made it fairly certain that its use would not be very advantageous. The method of testing for susceptibility to penicillin is simple and requires comparatively few hours. It gives a reasonably accurate indication of what effect the penicillin may have on the organisms in vivo. It has been found to be of little value in vivo when its use in vitro has shown very little inhibition of culture growth. The second case revealed no evidence of valvular damage other than that due to arteriosclerosis. Although his cultures were still positive on dismissal he was subjectively much improved, but soon began to lose ground rapidly. The third case is that of a young woman with a history of epistaxis, sore throats and joint pains, which account for her valvular damage.

The next three cases are of those fortunate individuals who, both subjectively and clinically, have recovered from subacute bacterial endocarditis. Three recoveries out of six cases place this number far above the average for either spontaneous recovery or cure through the use of the sulfa-compounds. These patients did receive some of the sulfa drugs. However, their cultures remained positive while it was being administered. In each of these cases tests were made in vitro to determine the susceptibility of the organism to penicillin. In each case it was found to be susceptible to weak solutions of the drug, and thus gave hope it would be effective in vivo.

Case 4. J. M., white, male, aged 16 years, developed rheumatic arthritis at five years of age and since then had recurrent pain in the joints, with fever, palpitation, epistaxis and frequent colds. He was admitted to the hospital in December 1937, with joint involvement, but at that time had no cardiac damage. Tonsillectomy was done in 1938. The diagnosis of myocarditis was made in June 1939. A faint diastolic apical murmur was heard in August 1940 when he had another attack of arthritis. In January 1942 a diagnosis of aortic insufficiency and mitral stenosis was made. In February 1943 he had another attack of arthritis. About June 8, 1944, he noticed pain in his left lower chest. A diagnosis of pneumonia was made and he was started on sulfathiazole. He recovered from this attack in eight or nine days. On June 17, 1944, he had a slight nose bleed. On June 19 he was admitted to the hospital com-

plaining of weakness and a tired feeling for the preceding two or three weeks. He also had some mild exertional dyspnea but no orthopnea or nocturnal dyspnea.

Examination. Physical examination showed him to be poorly nourished, with a temperature of 101° F., pulse 122, respirations 20, blood pressure 120 mm. Hg systolic and 30 mm. diastolic. He looked much younger than his stated 16 years. The eyes were essentially negative. The chest showed a rather marked Harrison's groove and a rachitic rosary. The heart was enlarged and there was a harsh, high pitched, short systolic murmur heard all over the precordium, best at the apex, and a harsh, high pitched, diastolic murmur in the aortic area, which could also be heard at the apex. The pulmonic second sound was loud and snapping. There was a Corrigan pulse with pulsating capillaries and pistol shot femorals. The liver could be demonstrated by percussion 3 cm. beneath the costal border but it could not be felt. The spleen was barely palpable.

Laboratory Reports. On admission, on June 19, the red blood cells were 3,180,000; hemoglobin 9 grams; sedimentation rate 33 mm. On June 23 the sedimentation rate had jumped to 138 mm. The white cell count varied from 10,000 to 18,000.

Roentgenogram showed the heart to be enlarged to the right and the left atrium showed very marked dilatation, displacing the esophagus to the right and posteriorly. Blood cultures taken on June 19 and June 21 showed a positive growth of *Streptococcus viridans* which was sensitive to penicillin. For the first 10 days of hospitalization he ran a spiking fever which averaged about 102° F. at its peak but one day went as high as 104°

Treatment. Penicillin was started on June 28 and he received 25,000 units intramuscularly in 2 c.c. of normal saline every two hours. On the third day of treatment the temperature dropped to normal and remained there for the duration of his hospitalization. He received a total of 4 million units of penicillin and was dismissed from the hospital on July 24, 1944. Additional blood cultures, two of which were taken during August, showed no growth. He was dismissed on 1 gram of sulfadiazine daily "for life." His last visit was August 25, 1944, at which time he was symptom free. His red blood cells then numbered 3,880,000; white blood cells 7,900; hemoglobin 11.5 grams.

Case 5. L. H., colored female, 20 years of age, was admitted to the hospital on February 10, 1944. At the age of six this patient had rheumatic fever with arthritis so severe that she used crutches for six months. In 1941 an aortic diastolic murmur was found and a diagnosis made of rheumatic heart disease with aortic insufficiency. Kahn tests in 1940 and 1941 were positive. In 1941 a lumbar puncture yielded negative spinal fluid. The day before admission to the hospital she complained of mild headache which lasted all evening. She also had some slight fever and pain in the knees when walking.

Physical Examination. Her temperature on admission was 103° F., pulse 120, respirations 22, and blood pressure 120 mm. Hg systolic and 60 mm. diastolic. She was not acutely ill and was moderately well nourished. There were no petechiae. No joints were involved except that the knees were somewhat painful on passive movement. The glands in the posterior cervical and axillary regions were palpable but not tender. The eyes showed some pulsating vessels in the fundi. The left border of dullness of the heart was 9 cm. to the left. A grade 2 systolic murmur was heard at the apex, transmitted to the axilla. There was a slight diastolic murmur heard at the secondary aortic area but none at the apex.

Laboratory Reports. Sedimentation rate was 51 mm.; white blood cells numbered 10,750, with 86 per cent polymorphonuclears. Kahn reaction was negative. The first blood culture yielded 165 colonies per c.c. of alpha hemolytic streptococcus. Fluoroscopic examination of the chest was indicative of rheumatic heart disease with mitral involvement. There was no suggestion of congestion or pleural fluid. Spinal fluid examination was negative. The electrocardiogram showed no significant findings.

Treatment was symptomatic for the first three days and patient was placed on sulfadiazine. Two days later the fever curve returned to normal and then rose to 99° F. and then to 102° and 103°, with strongly positive blood cultures. On the twelfth hospital day penicillin, 250,000 units a day intramuscularly, was started with individual doses every two hours day and night for 14 days. The day after this therapy was started the temperature returned to normal and until therapy was stopped on the twenty-sixth hospital day did not rise significantly. From the twenty-sixth to the thirty-second hospital day the temperature curve ran between normal and 100° F. and then came down to normal and stayed there. The patient felt greatly improved after therapy was stopped and gained in weight and strength. The day before therapy was begun there were 27 colonies of alpha hemolytic streptococcus per c.c. of blood and the day after therapy was started the organisms had completely disappeared. She was discharged from the hospital on March 21, 1944. On March 28, and again on April 11 blood cultures were still negative. Sedimentation rate also came down to 40 mm. in one hour on discharge, 34 mm. a week later, and 31 mm. two weeks thereafter. The white cell count was normal during the entire course of penicillin, it became slightly elevated when the penicillin was stopped and then fell to normal with the fever curve. During her course in the hospital she received two transfusions of 500 c.c. each, and also ferrous sulfate by mouth. Her red cell count was 5,000,000; hemoglobin 12 grams. When seen three weeks after discharge she was asymptomatic, feeling well and quite strong and ready to return to work. Six months later she was still well and symptom free and working daily without difficulty.

Case 6. T. A. S., white male, age 64, was admitted to the hospital on January 1, 1944, complaining of weakness of two months' duration. In July 1943 he had been told that he needed several abscessed teeth removed, and his local physician said his physical condition was satisfactory. Between July and October 19, one-third of his teeth were extracted, one or two at a time. Late in October he lost his appetite and energy, and was no longer able to work as long or as hard as usual. He had no pain at this time. Between October and December he had frequent night sweats. He had no chills or fever. These symptoms gradually progressed until December when he was confined to bed because of weakness. There was no dyspnea. His weight loss was approximately 30 pounds, decreasing from 150 pounds to 120 pounds.

Past History. He had an unknown fever of some sort when he was quite young. No other serious illnesses.

Physical Examination. He was a poorly nourished white male. There was a small petechial hemorrhage on the palpebral conjunctiva of the right lower eye lid. The heart was not enlarged to percussion. There was a distinct, soft, blowing systolic murmur heard over almost the entire precordium. The second sound was slightly accentuated but there were no murmurs. Blood pressure was 110 mm. Hg systolic and 70 mm. diastolic. Liver and spleen were not palpable.

Laboratory Reports. Urinalysis frequently showed a heavy trace of albumin and usually from 1 to 3 red blood cells per high power field. Red blood cell count on admission was 3,300,000; white blood cells 10,000; hemoglobin 10.7 grams. On January 12 his white cell count had risen to 21,350, but by February 2 had dropped again to 12,000. On February 15 it came down to less than 9,000 and remained there throughout his stay. Sedimentation rate on admission was 77 mm., rising as high as 104 mm. on January 12, 1944, dropping again to 100 mm. on February 2, 1944, and decreasing gradually to 60 mm. at dismissal. Between January 5 and January 11 four cultures were positive for *Streptococcus viridans.* On January 18 a culture showed inhibition of growth over half of the Petri dish with penicillin diluted 1:250 units per c.c. and 1 c.c. placed in a dish. A culture on January 22 showed six colonies. On January 24 the culture showed two colonies, on January 29 two colonies and from then on all cultures were negative, although they were taken

regularly at frequent intervals and eight were made. Electrocardiogram showed no definite evidence of myocardial damage. Neo-prontosil (intramuscularly) was started on the sixth day of hospitalization and was continued in what was considered adequate dosage until the administration of penicillin was begun. From the time of his admission on January 1 until the time penicillin was started on January 29 he had a spiking temperature averaging 102° F. but at times did become elevated to 103°. On January 29 he was started on penicillin and from then on his temperature stayed below 100° until the very day that the penicillin was stopped on February 12, and on that day he ran a temperature of 103° at 8 o'clock in the morning for some unknown reason. His temperature dropped then and remained between 98° and 99° for the duration of his hospital stay. He was dismissed from the hospital on March 6, 1944. At that time he weighed 131 pounds and had received a total of 4,225,000 units of penicillin.

Progress Notes. On January 9 several small petechiae were discovered in the left anterior chest wall. On January 14 there were two fresh hemorrhages in the right fundus, one medial and one lateral to the disc. There was a similar hemorrhage in the left eye superior to the disc. On the ninth he also developed an Osler's node at the tip of the left forefinger which was painful and tender. This disappeared within five days. On January 24 he had developed some petechiae in the left conjunctival sac and the hemorrhages in the eyes had resolved. On January 25 his condition became much worse; his speech was irrational and indistinct and he appeared disoriented, and had an aphasia. The cranial nerves were apparently intact; all the abdominal reflexes and cremasteric reflexes were absent. The pupils reacted rather sluggishly to light. At this time it was considered that he might have had an embolus from a vegetation to the left mid-cerebral artery. The following day he was better oriented and appeared to have partially recovered. On February 3 no marked changes were observed and the sedimentation rate was even more elevated than previously but the patient felt that his appetite was better.

Follow-Up. On March 22 his weight had increased to 148 pounds. His appetite was good. He had no fever and no complaints. The left border of cardiac dullness was 10 cm. from the midsternal line in the fifth left interspace. There was a rather loud systolic murmur but no diastolic murmur was heard. Blood pressure was 140 mm. Hg systolic and 76 mm. diastolic. Red blood cells numbered 3,830,000; white blood cells, 12,600; hemoglobin 12.2 grams. Sedimentation rate was 42.5 mm. in one hour. On April 19 he weighed 152½ pounds. December 25 he is quite well.

All of the above cases show evidence of earlier damage to the valves of the heart before the onset of the endocarditis. Cases 4 and 5 showed a long history of valvular damage of considerable extent, yet they were able to withstand the onslaught of bacterial invasion and to recover without much appreciable additional damage to the valves. Case 6 in particular presented a gamut of clinical manifestations varying from the slight fever, weakness and weight loss which accompanied the onset of the disease, down through progressive wasting away and loss of orientation through a cerebral accident and up again from the shadows to new life and health. One of the striking factors in these cases is the unusually large amount of penicillin required to produce a cure in these patients. Evans [8] found that it required 4,500,000 units to effect a cure in his patient. We too have found that far above the usual amounts of penicillin must be used. Two hundred to three hundred thousand units daily must be injected regularly every two hours, day and night until about four million units have been given. Herrell et al.[7] used a

continuous intravenous drip method to administer a total of 80,000 units daily. The use of continuous intravenous drip probably has the advantage of giving the patient a more uniform and constant concentration of penicillin in the blood, which is very desirable, than by the intramuscular injection every two hours. However, the difficulty of holding an arm quiet for the many days necessary to administer the treatment makes it appear easier on the patient if the intramuscular method is used.

The first two cases in our series received less than three million units of penicillin and the others received approximately four million or more units. This is far above the average doses required for the successful treatment of other conditions which respond to penicillin. Moreover, it must be continued in concentrated doses for a longer period of time than is necessary in the treatment of other penicillin-susceptible infections. None of the patients treated in this series suffered any reactions which could be attributed to the penicillin. Very few serious reactions have been reported during its use. Herrell [7] states that it can be used with safety even in severe anemia, leukopenia or even complete agranulocytosis. With the improved purity of penicillin even fewer reactions are likely to occur.

Summary

We have presented six cases of subacute bacterial endocarditis proved by repeatedly positive blood cultures in each case. Three of these cases were rather hopeless from the onset; the other three, although they appeared to be hopeless, nevertheless responded so well to penicillin therapy that they are still alive and well and without subjective or objective evidence of a bacterial endocarditis. The two adults are again working daily at their respective occupations and have gained in weight and strength. It is now six months since the dismissal of one from the hospital, and nine months or more for the other two patients. They will be followed carefully for some time to come.

It is felt that failure in some cases which have been reported in various journals may have resulted from insufficient concentration of penicillin, or an inadequate total dosage. All cases seem to require at least 4,000,000 units and now that it is more readily available commercially there should be no reason why even greater total dosage could not be used.

These three cures out of six cases are but a small number, and no accurate percentage of cures can be derived from this small series. However, it does show that in patients whose organisms are known to be susceptible to penicillin there can be cure even in such serious illnesses as subacute bacterial endocarditis. We know that the results of cure with penicillin will rise far above the 1 per cent of cases that recover spontaneously and we hope that it will also give a much greater percentage of cures than the 4.5 per cent to 15 per cent of cures obtainable with various combinations of sulfa drugs.

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INHALATION OF PENICILLIN AEROSOL IN PATIENTS WITH BRONCHIAL ASTHMA, CHRONIC BRONCHITIS, BRONCHIECTASIS AND LUNG ABSCESS: PRELIMINARY REPORT *

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The purpose of this communication is to present the results of an exploratory study on the technic, safety and clinical effectiveness of inhaling penicillin aerosol in patients with bronchopulmonary infection. Many questions concerning dosage of the drug, length of treatment and choice of apparatus require further investigation. Our preliminary findings are reported in order that other workers in this field may study this relatively simple method of local application of penicillin to the bronchi and lung parenchyma, since the response in some patients has been of an encouraging nature. That penicillin aerosol penetrates the lungs and may be recovered from the urine in rabbits and normal human beings was demonstrated by Bryson, et al.[1]

Historical

The administration of drugs by inhalation through the lungs has been employed for many years in patients with asthma and pulmonary emphysema. When a suspension of a substance is produced by the passage of air or oxygen through a nebulizer, the resulting mist is termed a "nebulin" or an "aerosol." It has long been known that particulate substances of small size penetrate the alveoli, and that the size of the particles is dependent upon the nature of the nebulizer used. The beneficial results of inhaling the nebulized solution of 1:1000 epinephrine in patients with asthma were reported some years ago by Heubner [2] and Lageder.[3] An important practical advance in this therapy was made by Graeser and Rowe,[4] who suggested the more concentrated 1:100 solution of epinephrine, employed in a hand bulb nebulizer that provided a fine suspension of the drug. In simplicity of technic, rapidity of action and relative freedom from constitutional side effects, this method of administration presented practical administration over injection of epinephrine by hypodermic. The use of 1

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per cent epinephrine and 1 per cent neosynephrine by continuous inhalation was studied by Richards, Barach and Cromwell [5] in patients with bronchial asthma and other clinical entities with bronchial constriction. The use of these substances has been found to be of clinical value not only in cases of bronchial asthma and pulmonary emphysema,[6] but also in pneumonia and pulmonary edema [7, 8] and in irritant gas poisoning.[9, 10] A more stable and less irritating suspension of epinephrine is obtained if a 5 to 20 per cent solution of glycerin is added, as shown by the classical study of Abramson,[11] but the concentrations of penicillin used in this investigation are high enough not to require addition of glycerin. Lockey [20] also found that the addition of 5 per cent glycerin to a 1 per cent epinephrine solution resulted in less irritation and dryness of the throat.

The employment of chemotherapeutic agents as aerosols had the theoretical advantage of a high local concentration with a relatively low blood level of the drug, since nebulized solutions penetrate to the depths of the lungs.[2] Castex, Capdehourat and Pedace demonstrated that a 5 per cent solution of sulfanilamide resulted in clinical improvement in cases of bronchopulmonary suppuration.[12, 13] Krueger, et al.[14] showed that the material was uniformly distributed through the alveoli of the lungs by employing India ink in monkeys and mice. Chambers et al.[15] developed a method of preparing minute microcrystals of sulfathiazole which were sprayed into the lungs by an atomizer supplied with compressed air. They demonstrated that significant amounts of sulfathiazole can be absorbed through the lungs with the production of high blood levels of this drug. The inhalation of the nebulized solution of promin was shown to prevent the development of experimental tuberculosis in guinea pigs by Barach et al.[16] Promin solution has recently been used as an aerosol in patients with pulmonary tuberculosis by Edlin et al.[17] Stacey [18] reported marked improvement after inhalation of nebulized sulfathiazole solutions in patients with bronchiectasis.

The use of penicillin as an aerosol was suggested by Bryson, Sansome and Laskin.[1] Since penicillin is known to be bacteriostatic in extremely high dilutions, inhibiting the growth of hemolytic streptococci in quantities as low as 0.01 microgram per c.c., the potential value of inhaling a penicillin aerosol was considered likely. The efficacy of local instillation of penicillin solution in patients with empyema due to pneumococcus infection indicated that this drug was active in the presence of blood and pus. Penicillin is not inactivated by the presence of para-amino-benzoic acid in purulent exudates, in contrast to the sulfonamides.[19] Bryson et al.[1] showed that penicillin aerosols could be recovered from the lungs of rabbits. With a rebreathing bag oxygen mask nebulizer apparatus 3.2 per cent of 25,000 units of penicillin aerosolized in the mask were recovered in the urine during the first 12 hours after inhalation, but when a human subject inhaled the penicillin for 15 seconds and held his breath for 15 seconds thereafter these authors found that 60 per cent of the aerosolized penicillin was recovered in the urine dur-

ing a 12 hour period, which compared favorably with an average recovery of 60 per cent after intravenous injection. It is evident, however, that patients suffering from bronchial and pulmonary disease would not generally be able to hold their breath for a prolonged period of time.

In this communication various clinical methods of inhaling penicillin aerosol were tried. The initial results obtained in a series of patients with bronchial asthma complicated with bronchial infection, bronchiectasis, lung abscess and pulmonary emphysema with fibrosis will be presented.

The consideration of the optimal duration of treatment was subordinated to the primary purpose of determining the safety and early response to this chemotherapeutic approach in 20 patients, since the supply of the drug was limited. A small number of experiments on animals was performed to determine the possible irritating effect on the bronchi and lung parenchyma and the protective value of penicillin aerosol in systemic infection.

Methods

In the routine use of nebulinized solutions of epinephrine and neosynephrine the end of the nebulizer is held within the partly opened mouth and the patient inhales the aerosol as it is continuously produced by a stream of 5 liters per minute of oxygen passing through the nebulizer. During the expiratory cycle the nebulin of the drug passes into the outside air. In order to overcome an undue loss of penicillin aerosol an oxygen mask nebulizer apparatus was first employed in which the open end of the nebulizer was inserted through the mask between the lips of the patient. The aerosol of penicillin was then inhaled during inspiration and the aerosol remaining in the exhaled air was delivered into a rebreathing bag. A considerable portion of the drug condensed in the rebreathing bag which could not be easily re-used. Therefore, an enlarged glass nebulizer was substituted for the mask to collect penicillin in the exhaled air for rebreathing.

The volume and shape of the nebulizer were ultimately changed by fusing a 1000 c.c. glass bulb to the upper surface of the nebulizer. The glass tube from the nebulizer was lengthened and inclined upwards. The purpose of this modification was to collect within the enlarged nebulizer that part of the penicillin aerosol that remained in the expired air and to prevent excessive condensation on the inner surface of the glass bulb. The nebulizer * employed produced a suspension in which the majority of the particles were smaller than 1 micron.

In order to produce penicillin aerosol only during the inspiratory cycle a glass or metal Y tube was inserted in the rubber tubing between the oxygen regulator and the nebulizer. In operation, the open end of the Y tube is covered by the thumb of the patient (or nurse) before the start of inspiration and released before the end of inspiration. If ordinary respiration is adopted, the particles of penicillin are apt to be in contact with the bronchial

* The nebulizer is made by the Vaponefrin Co., Upper Darby, Pa.

surface for a longer period of time than if deep inhalations and breath-holding are employed. However, under the latter conditions higher blood levels are obtained, since the drug is then absorbed from the expanded alveolar surface. When the local deposition of the drug on the bronchial wall is sought, the blood level may be of secondary importance. On the other hand, in lung abscess deep breathing may result in better penetration of the cavity if the bronchi are enlarged by expansion of the chest. The size of the particles is another factor that merits consideration. The larger particles settle on the upper air passages and the smallest sized ones penetrate to the alveoli. The nebulizer that produced a majority of particles under one micron was selected in this study. The flow of oxygen is now generally set at 8 liters per minute. This may vary between 4 and 10 liters per minute depending upon the length of time which is considered optimal for nebulinization of the penicillin solution. The mouth is closed about the end of the nebulizer which is inserted over the tongue for about two inches. The carburator (or extra orifice in the nebulizer) is left open.

The development and trial of modifications of apparatus for inhalation of penicillin aerosol are proceeding. An automatic production of penicillin aerosol only during the inspiratory cycle is accomplished by a specially constructed demand valve apparatus which does not require the coöperation of the patient.[21] The small size (ordinary) nebulizer may also be employed, provided it is of the type that produces particles that are mostly under 1 micron in diameter, such as the Vaponefrin or the DeVilbiss No. 40 nebulizer. The nebulizer with an added 1000 c.c. volume makes possible the reinhalation of some of the aerosol in the patient's expired air together with that nebulized during inspiration. The attachment of the glass one liter bulb is so arranged as to prevent the aerosol formed during inspiration from entering this chamber, and in that way wasteful condensation of the drug is avoided.

The concentration of penicillin employed varied between 2,000 and 100,000 units dissolved in 1 c.c. of physiological saline. A concentration of 20,000 units per c.c. was employed in the early part of this investigation. More recently, dilutions of 40,000 to 50,000 units per c.c. were used. The solution is made by inserting 2 c.c. of 0.85 per cent saline into the standard bottle containing 100,000 units of penicillin and withdrawing 1.0 c.c. for each treatment in a sterile tuberculin syringe. In order to avoid waste of the penicillin 0.5 c.c. of normal saline is inserted into the original bottle when it is empty and a dilute solution of the penicillin that clings to the side of the glass is removed and used. An illustration of the apparatus is shown in the accompanying photograph (figure 1).

In infants and small children penicillin was at first administered by a catheter inserted in the oropharynx. Since the larger sized particles will condense in the catheter if it is taken directly from the nebulizer and thereby obstruct the flow of the aerosol, an empty bottle trap was inserted between the nebulizer and the tube that leads to the rubber catheter. A small amount of penicillin solution is condensed in the flask in this way and the remainder

of the nebulin consisting of particles of small size will now penetrate a No. 10 or No. 12 French catheter.

In adults penicillin administered by oropharyngeal insufflation does not result in as high blood levels as are produced by the oral method previously described. In infants and small children treated by the catheter method

FIG. 1.

beneficial clinical results as well as the presence of traces of penicillin in the blood have now been demonstrated. Since local deposition on the bronchi may be the chief intention of penicillin aerosol administration, the blood level is not the main factor. A mask nebulizer apparatus is now also being used in children.*

* A separate report of the studies in children will be referred to later.

Experimental and Clinical Results

The possibility of irritation of penicillin aerosol when introduced into the lung was subjected to investigation. When small amounts of penicillin were inhaled in a solution made of distilled water, coughing was noted. It was then found that inhalation of distilled water was irritating both to normal subjects and patients, due to its hypotonicity, and that normal saline could be inhaled without subjective experience of irritation. Penicillin was then uniformly dissolved in physiological saline. In four of 20 patients the possibility of irritation due to inhalation of penicillin aerosol presented itself. In one patient with bronchial asthma, increased cough was noted at the end of seven days' inhalation of 200,000 units per day in a concentration of 40,000 units per c.c. However, it was difficult to tell whether this was due to the penicillin aerosol or whether the patient had acquired an intercurrent infection as the result of a cold. In some patients coughing is produced immediately due to the physical effect of the solution itself and to deep breathing. This is not considered an irritant effect since it occurs with 0.25 per cent neosynephrine. In a second patient who had had bronchiectasis and a chronic lung abscess for 16 years there appeared to be a diminution of the peribronchial shadows at the end of two weeks' inhalation of penicillin aerosol, but at the end of one month of inhalation of penicillin aerosol the shadows around the bronchi by roentgen-ray appeared to be slightly increased. The patient also complained at this time of a sensation of irritation at the upper sternal margin. Another patient with bronchiectasis experienced substernal soreness at the end of five days' inhalation of penicillin aerosol, and noted at the same time urticaria on the thigh.

A fourth patient, who had an acute lung abscess, felt a slight irritation under the sternum at the end of seven days' inhalation of penicillin aerosol. However, roentgen-ray showed a disappearance of a fluid level and only a vague outline of a previously sharply defined cavity at this time. In 16 other cases treated for periods of seven days to one month, no subjective or objective manifestations of irritation were encountered. In 10 normal and miscellaneous subjects, inhalation of penicillin between 20,000 and 100,000 units per c.c. resulted in no sensation of irritation. In all the cases that complained of substernal irritation, the sensation disappeared on the following day. In three subjects slight soreness of the tongue or gums was noted, and in one of these patients the teeth were said to be shiny, and the tartar apparently removed.

Roentgen-ray examination was made before and after penicillin aerosol therapy not only to determine whether improvement occurred, but especially to detect any signs of inflammation or edema which might have taken place as the result of penicillin aerosol. The roentgen-ray of the lungs did not reveal any evidence of irritation except possibly in the case of bronchiectasis referred to above in which the changes were slight and may not have been due to the drug.

Inhalation of penicillin in aerosol form may perhaps produce transient irritation in the trachea in some instances. The majority of the treated cases (16 of 20) made no complaint of this nature. In the patient with bronchiectasis who was treated for one month with inhalation of 150,000 units daily, 40,000 units per c.c., there was no subjective complaint and repeated roentgen-rays showed no sign of an irritant effect of the drug. The possibility that the lung parenchyma is irritated by the aerosol appears to be remote. The larger sized particles in the aerosol are more apt to precipitate in the upper air passages and may account for the sensation of soreness under the sternum that was mentioned in the cases referred to above. However, the symptom was slight and transient. The soreness of the tongue may have come from solution inadvertently spilling into the mouth.*

The possibility of allergic reaction to the drug must be borne in mind, especially in patients with asthma, although no systemic manifestations of this kind have been observed. In two patients who received penicillin aerosol for three days an urticarial eruption was encountered. However, this disappeared in two days even though penicillin inhalation was carried on for two and six days thereafter.

Animal Experiments

Experiments were performed on rats to ascertain whether penicillin could be absorbed effectively by the inhalation route. White rats, weighing from 150 to 200 gm. each, were injected with 0.1 c.c. of a rat culture of hemolytic streptococcus. One group was kept as controls, a second received penicillin by intramuscular injection and a third group inhaled penicillin aerosol. In the latter group the heads of rats were placed in glass "helmets" into which penicillin aerosol was passed by means of a stream of oxygen flowing continuously through a glass nebulizer containing the penicillin dissolved in normal saline. After the desired amount of penicillin had been nebulized, it was followed by 1 to 2 c.c. of normal saline in order to salvage the penicillin condensed on the walls of the nebulizer. The flow of oxygen used was 4 liters per minute, and the amount of penicillin administered to each rat varied from 10,000 to 25,000 units.

* Further observations were made on the possible irritating effect of penicillin. The effect on normal rats of inhalation of sodium penicillin in a concentration of 50,000 units per c.c. was studied by administering the aerosol in the hood apparatus, 20,000 units daily for five successive days. Four treated animals were compared to four animals to whom a similar volume of normal saline was administered and to four additional untreated control animals. In addition a total of 10 rats, including two controls, were treated by 5 inhalations on successive days of 1 c.c. neosynephrine, sulfathiazolate, sulmefrin, 20 per cent potassium iodide solution, and 2.5 per cent sulfadiazine in ethanolamine solution. Microscopic section of the lungs of the penicillin treated animals showed no significant differences as compared to the animals receiving saline, the untreated controls, and the miscellaneous group. In each series scattered areas of congestion, edema, atelectasis and occasional hemorrhages were observed. In no instance was there inflammatory change in the bronchi.

In a recent series of patients calcium penicillin has been found to produce superior aerosol than the sodium salt. It is uniformly preferred by patients since it has less odor and it is much less apt to provoke coughing, even in patients who cough after inhalation of sodium penicillin.

With this method of administration much of the drug was lost by condensation on the glass "helmets" and on the animals' fur, as well as by escape from the "helmet" with the stream of oxygen.

TABLE I

Effect of Penicillin by (A) Intramuscular Injection and (B) Inhalation as Aerosol on the Mortality of Rats Infected Intraperitoneally with a Fatal Dose of Hemolytic Streptococcus Culture

	Penicillin Dosage in Units	No. Rats Used	Mortality		Survival Time in Hours
			No.	Per Cent	
Controls	0	31	31	100	27
(A) Intramuscular Injection	10,000	6	1	16.6	89
	15,000	3	0	0	—
	20,000	16	1	6.2	143
	25,000	3	2	66.0	106
Total		28	4	14.4	53
(B) Inhalation of Aerosol	10,000	8	6	75	22
	20,000	16	11	69	62
	25,000	7	2	28.6	103
Total		31	19	61.3	53

Table 1 shows the results of such experiments on a total of 90 rats. Of 31 control animals, all died, the average length of life after injection of 0.1 c.c. hemolytic streptococcus culture being 27 hours. Of 28 rats given penicillin by injection only four (14.4 per cent) died, and these animals lived an average time of 117 hours after infection. In the third group of 31 rats given penicillin by inhalation 19 (61.4 per cent) died, living an average time of 53 hours after infection. It is evident, therefore, that penicillin given by inhalation may protect rats against systemic hemolytic streptococcus infection, but that owing to obvious loss during its administration, the protection is less effective than a comparable dose injected intramuscularly. With larger doses penicillin aerosol is more effective. When 10,000 units of penicillin were administered 75 per cent of the rats died, surviving only 22 hours, while with 25,000 units only 28.6 per cent died, surviving on an average of 115 hours after infection. As indicated above, only 12,500 units were available during the inspiratory cycle of respiration.

The concentration of the penicillin solution used seemed to make little difference in the results. Concentrations varying from 1,000 to 20,000 units per c.c. were used, but no correlation with the mortality rate could be noted in this small series.

In order to determine whether inhalation of penicillin aerosol resulted in pathological changes in the lungs or bronchi a study was made of the lungs of 19 rats that had previously inhaled penicillin aerosol. The total amount of penicillin inhaled varied from 20,000 to 115,000 units per rat, given in

concentrations varying from 2,000 to 40,000 units per c.c. of solution vaporized. In some cases the inhalations were spread over four or five days, and in others the doses were given in a single inhalation. The rats were usually killed 18 to 20 hours after the last inhalation, but in a few cases were sacrificed immediately following inhalation. They were killed either by a blow on the head, by immersion in an atmosphere of nitrogen, or by injection of an immediately lethal dose of nembutal. Thirteen control rats, receiving no penicillin, were sacrificed similarly.

Microscopic sections of the lungs of the normal rats revealed at times scattered areas of edema and congestion, and occasional patches of atelectasis. The lungs of rats killed by a blow on the head or by nitrogen showed occasional small hemorrhages, possibly caused by the method of sacrifice of the animal.

The penicillin treated lungs showed similar findings, but the edema and congestion appeared somewhat more marked and the atelectatic patches were more frequently noted. As in the control lungs, occasional slight hemorrhages were found in the lungs of those animals killed by a blow on the head or by nitrogen. In one control lung and in two penicillin treated lungs, signs of bronchopneumonia were observed, but these appeared to be of too long duration to be related to the experimental procedure.*

The differences between penicillin treated and control lungs were, however, very slight, and did not appear to indicate an irritant effect of penicillin. Furthermore, the small and larger bronchi showed no sign of inflammation in either group. It is not yet known whether the slight differences shown were caused by the process of inhaling an aerosol, without any specific action by the penicillin. The control animals were not held in the glass "helmets" and did not inhale normal saline, as is being contemplated in a new series of experiments.

Effect of Penicillin Aerosol on Predominating Organisms in the Sputum

The effects of inhalation of penicillin aerosol on the pathogenic organisms recovered from the sputum in 18 tested patients is shown in table 2. It will be seen that in 15 cases the culture of the sputum after penicillin therapy did not show the previously determined organism and in one patient in whom the pretreatment specimen was lost, no pyogenic organisms were found after inhalational therapy. The second culture was taken generally 24 hours after termination of penicillin aerosol treatment. In one instance the organism identified from the sputum was not found to be sensitive to penicillin although in this case there appeared to be a marked regression of the lung abscess by roentgen-ray. In the eight other tested cases the recovered organisms were found to be sensitive to penicillin although not generally as sensitive as the standard organism. In some patients who were treated for

* Dr. Homer D. Kesten kindly aided in the interpretation of the sections.

one week with inhalation of penicillin aerosol the pathogenic organism recurred later, with reappearance of symptoms. Since this communication records in the main the early results of inhalation of penicillin aerosol, the length of time these organisms, found in the sputum prior to treatment, remained absent from the patients' expectoration will be presented in a later report.

Penicillin Blood Levels During and After Inhalation of Penicillin Aerosol

The blood level of penicillin was determined at different times during the first hour or more after inhalation of the aerosol in the majority of patients, as shown in table 3. Although the dosage varied in certain patients the blood level as seen in the table represents that which occurred after the dose most generally used in the individual patient. It will be seen that in the largest number of patients blood levels of .01 to .04 were found during the first 15 minutes to one hour after the inhalation. In two patients a blood level of .14 to .18 was found one-half hour after inhalation of penicillin.

Table II

Effect of Inhalation of Penicillin Aerosol on Organisms Recovered from the Sputum

Case No.	Sputum Culture		Sensitivity of Sputum Organism to Penicillin
	Before Treatment	After Treatment	
1	Hemolytic *Staph. aureus*	Unidentified Gram + diplococci	Neither organism sensitive to penicillin
2	*Strep. viridans*	*B. aerogenes*	*Strep. viridans* ¼ as sensitive to penicillin as standard organism.
2	Pneumococcus, type 31	No pneumococcus *B. coli* predominate	Pneumococcus considered sensitive to penicillin.
4	Pneumococcus, type 3	No pneumococcus *B. aerogenes*	Pneumococcus ½ as sensitive to penicillin as standard organism.
5	*Strep. viridans*	No *Strep. viridans* *B. aerogenes*	*Strep. viridans* ¼ as sensitive to penicillin as standard organism.
6	Hemolytic strep. L5	No hemolytic strep. *Strep. viridans*	Hemolytic strep. equal to standard in sensitivity.
7	*Strep. viridans*	*B. aerogenes* in pure culture	—
8	Hemolytic strep., B Hemolytic *Staph. aureus*	*B. proteus*	Hemolytic strep. ¼ as sensitive to penicillin as standard organism.
9	Hemolytic and non-hemo. strep., *Staph. aureus*	—	—
10	Hemolytic *Staph. aureus* *Strep. viridans*	*B. aerogenes*	—

TABLE II—*Continued*

Case No.	Sputum Culture		Sensitivity of Sputum Organism to Penicillin
	Before Treatment	After Treatment	
11	Gram + diplococcus	*B. coli*	Slightly more sensitive to penicillin than the standard organism.
12	Hemolytic *Staph. aureus* *Strep. viridans*	*B. aerogenes*	—
13	*Strep. viridans*	*B. aerogenes*	*Strep. viridans* ½ as sensitive to penicillin as standard organism.
14	*Strep. viridans*	*B. aerogenes*	
15	*Strep. viridans* *Staph. aureus* Hemolytic strep.	No pneumococcus *B. coli*	Hemolytic strep. ½ as sensitive to penicillin as standard organism.
16	Hemolytic strep. *Strep. viridans* *Staph. albus*	No pneumococcus *B. aerogenes*	*Strep. viridans* ½ as sensitive to penicillin as standard organism.
17	*Strep. viridans*	No pneumococcus *Strep. viridans**	—
18	—	No pneumococcus No staph. No strep.	—
19	*Strep. viridans*	No pneumococcus *B. aerogenes*	—
20	Hemolytic *Staph. aureus* *Strep. viridans*	No pneumococcus Gram—bacillus predominating	Hemolytic *Staph. aureus* equal in sensitivity to standard organism. *Strep. viridans* ½ as sensitive as standard organism.

* Sputum culture taken 7 days after termination of penicillin aerosol therapy.

In general, higher levels of penicillin in the blood were obtained after higher dosages, although in cases in which a large amount of purulent expectoration was present and in cases with pulmonary fibrosis, the blood level tended to be lower. Considerable variation may be accounted for on the basis of differences in the breathing pattern of the individual patient. Higher blood levels will be obtained if the patient is instructed to take a deep breath during the inhalation of the aerosol and hold it for several seconds before exhaling. In all instances the inhalation of penicillin aerosol was followed by at least minimal amounts of penicillin in the blood, indicating that the aerosol reached the alveoli.

In table 4 the serum penicillin levels are reported after the onset of nebulinization of the drug in four patients with miscellaneous disease without pulmonary pathology. The excretion of penicillin in the urine is also shown. It will be observed that in these patients generally higher blood levels were found and that penicillin was obtained in the blood as early as five minutes after the onset of inhalation of the drug.

TABLE III

Penicillin Blood Levels after Inhalation of Aerosol

Case No.	Dose of Single Inhalation	Concentration Units per c.c.	Blood Level of Penicillin Units per c.c. After Inhalation						No. Blood Levels
			0–15 min.	30 min.	45 min.	1 hour	1½ to 1¾ hrs.	1¾ hrs. to 2 hrs.	
1	40,000	17,000	0.004	0.02					2
2	40,000	20,000	0.01	0.07	0.01				4
3	40,000	20,000	0.02		0.02				2
4	20,000	20,000							0
5	20,000	20,000		0.01		0.01			2
6	20,000	20,000	0.02	0.02		0.02			7
7	70,000	35,000	0.02	0.14	0.14	0.07			4
8	50,000	17,000	0.004	0.02	0.004				10
9	40,000	40,000	0.09	0.18	0.09	0.04			19
10	50,000	50,000	0.03		0.02				4
11	40,000	40,000	0.01	0.03	0.01	0.02			5
12	40,000	40,000							0
13	40,000	40,000	0.02	0.02	0.01				4
14	40,000	40,000	0			0.01			3
15	50,000	50,000	0.03	0.02		0.02	0.02	±	7
16	50,000	50,000							0
17	50,000	50,000	0.02	0.02	0.02	−0.02		±	7
18	50,000	50,000		0.03		0.02			2
19	100,000	100,000	0.01						7
20	50,000	50,000		0.03		0.03			2

The effect of inhalation of 100,000 units in 1 c.c. is illustrated in case D, in which the high blood level of 0.4 unit was found at five minutes, 20 minutes and 45 minutes after the beginning of aerolization of penicillin; at 105 minutes .05 unit was obtained in the sample taken at that time. This response indicates that a very high blood level can be obtained, if desired,

TABLE IV

Blood Levels and Urinary Excretion of Penicillin during and after Inhalation of Aerosol in Subjects without Pulmonary Disease

Case No.	Concentration of Penicillin Units per c.c.	Total Dosage Inhaled In Units	Serum Penicillin Levels After Aerolization Started (in Minutes)					
			5 to 10	15 to 30	35 to 45	50 to 65	70 to 85	90 to 105
A	40,000	40,000	.1	.1	.05	.05	0	0
	40,000	40,000	.05	.05		0		0
	40,000*	40,000		0	0	0	0	0
	100,000	50,000	0	.025	0	0	0	0
B	40,000	40,000	0	0	.0125	.0125	0	
	40,000	60,000	0	.0125	.025		.0125	
C	40,000	40,000	.025	.1	.05	.025	.025	
	13,333	40,000	0	0	0	0	0	0
D	100,000	50,000	.05	.2	.05	0	0	0
	100,000	100,000	.4	.4	.4	.2	.1	.05

* Oropharyngeal aerosol.

TABLE IV—*Continued*

Blood Levels and Urinary Excretion of Penicillin during and after Inhalation of Aerosol in Subjects without Pulmonary Disease

Units of Penicillin Excreted				Excretion of Penicillin During 24 Hours in Per Cent of Total				Excretion of Penicillin in Relation to Total Amount Eliminated %		
1 hour	2–6 hrs.	7–24 hrs.	Total	1 hr.	2–6 hrs.	7–24 hrs.	Total	1 hr.	2–6 hrs.	7–24 hrs.
2,940	995	250	4,185	7.4	2.5	.63	10.5	70.2	23.8	6
431	92	0	523	1.1	.2		1.3	82.4	17.6	
1,863	1,183	0	3,046	3.7	2.4		6.1	61.1	38.9	
980	2,187	539	3,706	2.5	5.5	1.3	9.3	26.5	59.0	14.5
1,418	3,675	392	5,485	2.4	6.1	.7	9.2	25.8	67.0	7.2
4,620	2,703	0	7,323	9.2	5.5		14.7	63.1	36.9	
7,612	11,100	1.058	19,770	7.6	11.1	1.1	19.8	38.5	56.1	5.4

almost immediately by this method at the onset of treatment when a sufficiently large dose is used. It may also be mentioned that no sign of irritation was manifest by the patient as a result of inhaling the high concentration of 100,000 units in 1 c.c. In Case A inhalation of 40,000 units in 4 c.c. by means of a catheter placed in the oropharynx was followed by no evidence of penicillin in the blood. In another patient treated in the same way 0.02 unit was recovered at the end of one-half hour. In the infants and children treated in this way similar small amounts of the drug (.01 to .02) were found. The blood level is lower in shallow breathing, or ordinary respiration, but the local impingement of penicillin on the bronchi may be greater. A deep inspiration of 1000 c.c. carries most of the aerosol beyond the tracheobronchial passageway, a volume of approximately 140 c.c., into the alveoli, where maximal blood absorption necessarily takes place. However, a deep breath which is held several seconds allows more penicillin to fall out of solution on both the bronchi and alveoli, with less possibility of loss in the expired air.

The excretion in the urine of penicillin during a 24 hour period following inhalation of the aerosol is shown in table 4 to vary between 10 and 20 per cent of the total amount administered. The largest percentage excretion of the drug in the urine generally takes place within the first hour in patients without pulmonary pathology, although substantial amounts are still recoverable two to six hours afterwards. Small amounts of penicillin are found in the urine from seven to 24 hours following the inhalation of the drug. Further studies are in progress in patients with bronchopulmonary disease.

It is evident that a lower excretion of penicillin takes place after administration of the drug by inhalation than by intramuscular injection. By the

TABLE V

Effect of Inhalation of Penicillin Aerosol in Bronchial and Pulmonary Infection

Case No.	Age and Sex	Diagnosis	Duration of Disease	Average Daily Dosage (Units of Penicillin)	Length of Treatment (Days)
1	35 F	Lung abscess Rheumatic heart disease Pulmonary infarction	7 weeks	200,000	8
2	36 M	Bronchial asthma Chronic bronchiolitis Pulmonary emphysema	25 years	160,000	9
3	59 F	Acute bronchitis Bronchial asthma Pulmonary emphysema	3 days (13 years)	120,000 200,000*	7 7*
4	40 F	Bronchial asthma Chronic bronchitis Pulmonary emphysema Pulmonary fibrosis	28 years	200,000	5
5	43 M	Bronchiectasis Lung abscess Pulmonary emphysema Pulmonary fibrosis	15 years	100,000	7
6	52 M	Bronchial asthma Pulmonary emphysema Pulmonary fibrosis Cardiac hypertrophy Auricular fibrillation	25 years	100,000	7
7	60 F	Bronchial asthma Bronchiolitis	8 months	250,000 200,000*	8 10*
8	24 M	Bronchiectasis Lung abscess	16 years	200,000	30
9	29 F	Bronchiectasis Pulmonary emphysema Lung abscess	23 years	148,000	35
10	61 M	Pneumonitis Lung abscess (?)	6 months	200,000	8

* Second course of penicillin aerosol therapy.

TABLE V—*Continued*

Effect of Inhalation of Penicillin Aerosol in Bronchial and Pulmonary Infection

CLINICAL COURSE AFTER PENICILLIN AEROSOL
A case of lung abscess of seven weeks' duration, treated previously for one month with intramuscular injection of 160,000 units of penicillin daily, manifested a residual cavity with fluid level. After one week of penicillin aerosol, cavity margins became indistinct, fluid level disappeared. Ultimate recovery. Penicillin intramuscularly subsequently.
Patient had had severe asthma since the age of eight, which was markedly relieved one year previously with aminophyllin and a bronchial relaxation program. Considerable cough and dyspnea on exertion remained, accompanied by both sibilant and moist râles in the lungs. After one week of penicillin aerosol therapy the symptoms were markedly improved with an increase in vital capacity from 3,800 to 4,500 c.c. No change in roentgen-ray of the lungs. Three weeks later the patient developed a bronchopneumonia due to pneumococcus, was treated with sulfadiazine and recovered, although did not maintain original improvement apparently produced by penicillin aerosol.
For nine years this patient had taken hypodermic adrenalin most of the time every three to 10 hours. Following inhalation of penicillin aerosol she required no epinephrine for two months then gradual increase in cough and wheezing took place. A course of penicillin by intramuscular injection was given without improvement and a second course of penicillin aerosol for seven days was also administered with no significant improvement.
In this patient with advanced respiratory disease there was a moderate clinical improvement but an infection occurred three days after the patient left the hospital with recurrence of symptoms of cough and dyspnea.
In this patient with bronchiectasis, cavities and advanced fibrosis only little improvement took place, with an increase in vital capacity from 1,800 to 2,000 c.c. The roentgen-ray before and after treatment showed no change in the lung picture.
Slight clinical improvement appeared to take place with an increase in vital capacity from 1,300 to 1,700 c.c. There were fewer râles in the chest but no significant decrease in dyspnea on exertion. Roentgen-ray before and after treatment showed no change.
Striking clinical improvement followed inhalation of penicillin aerosol with marked decrease in dyspnea and in the number of sibilant and crepitant râles; vital capacity increased from 1,000 to 1,900 c.c. No change on roentgen-ray before and after treatment. The patient maintained improvement for two and one-half months when cough and dyspnea and râles recurred. A second course of penicillin aerosol therapy for 10 days was followed by almost complete freedom from dyspnea, asthma and complete clearing of all râles.
No clinical improvement could be observed in this patient who had had a lung abscess and bronchiectasis for 16 years. Lobectomy was subsequently performed with recovery.
No significant improvement took place, although sputum decreased from 40 grams to 14 grams and became more fluid, with less purulent material. Cough was less frequent, but there was no change in roentgen-ray of the lungs before and after treatment.
This patient with an undiagnosed pneumonitis had had one month of intramuscular penicillin with little or no benefit. After eight days of penicillin aerosol, temperature declined from 103 to 100° F. with marked clinical improvement. On discontinuance of the drug temperature recurred moderately and a course of combined aerosol and intramuscular penicillin was followed by a decline in temperature and clinical improvement with signs of clearing of infiltration by roentgen-ray.

TABLE V—*Continued*

Case No.	Age and Sex	Diagnosis	Duration of Disease	Average Daily Dosage (Units of Penicillin)	Length of Treatment (Days)
11	60 F	Bronchiolitis Bronchial asthma Bronchopneumonia Pulmonary emphysema Pulmonary fibrosis	25 years	200,000	12
12	57 M	Bronchial asthma Bronchiectasis	18 years	200,000	7
13	62 F	Bronchial asthma Pulmonary emphysema Chronic bronchitis	25 years	200,000	7
14	62 M	Bronchial asthma Bronchiolitis Pulmonary emphysema Chronic bronchitis Bronchiectasis	20 years	200,000	8
15	42 F	Bronchial asthma Chronic bronchitis Pan-sinusitis	9 years	200,000	10
16	59 M	Bronchiectasis, bilateral, advanced Pulmonary fibrosis	7 years	200,000	5
17	56 F	Bronchiectasis Pulmonary fibrosis	5 years	200,000	6
18	53 M	Bronchial asthma Chronic bronchitis	15 years	200,000	5
19	65 M	Lung abscess, acute	5 weeks	250,000	10
20	71 F	Bronchial asthma Chronic bronchitis Sinusitis	4 years	250,000	8

TABLE V—*Continued*

CLINICAL COURSE AFTER PENICILLIN AEROSOL
A gradual decrease in temperature occurred over a period of six days of penicillin aerosol therapy with ultimate complete absence of cough, asthma and expectoration. Following a cold and acute sinus infection symptoms recurred one month after treatment, namely, cough, asthma and expectoration.
Striking improvement with disappearance of asthma and cough, and clearing of râles took place after seven days in a patient previously adrenalin fast and suffering from intractable asthma and bilateral bronchiectasis. Patient was well for one month; recurrence of symptoms was treated with penicillin by intramuscular injection for seven days and by inhalation for 12 days without improvement.*
Moderate clinical improvement during the first six days of therapy with increased cough on the seventh day and subsequent increased betterment following one week of intramuscular penicillin. The moderate improvement obtained has persisted for three months. No change in roentgen-ray of the lungs before and after treatment.
Definite decrease in cough, expectoration and dyspnea followed inhalation of penicillin aerosol therapy. No change in roentgen-ray of lungs before and after treatment. One month later recurrence of symptoms of cough, expectoration and dyspnea took place of intensity comparable to that before penicillin-aerosol therapy.
The patient had been in the hospital for three and one-half weeks prior to treatment requiring 12 to 13 injections of adrenalin a day. However, on a bronchial relaxation program of aminophyllin and demerol the symptoms of asthma were relieved although not entirely absent prior to inhalation of penicillin aerosol. Improvement continued so that the patient required no adrenalin whatsoever, but took aminophyllin 0.3 twice daily. Symptoms of asthma continue to be absent for two months, but the result cannot be ascribed to penicillin aerosol therapy.
This patient showed no improvement from one week of penicillin injected intramuscularly nor from inhalation of neosynephrine-sulfathiazole mixture, but appeared to manifest a quite marked decrease in dyspnea and cough after four days of inhalation of penicillin aerosol. He complained of soreness in the chest at the end of five days and the treatment was stopped; the patient was discharged, temporarily improved.
This patient suffered from continuous dyspnea for five years prior to treatment and both cough and dyspnea were marked at rest. After two days of inhalation of neosynephrine-sulfathiazole mixture a definite clinical improvement took place which continued with penicillin aerosol and at the end of therapy the patient was completely relieved of shortness of breath for the first time in five years. The result was striking, but was initiated by the neosynephrine-sulfathiazole mixture and appeared to be still further benefited by penicillin aerosol. Freedom from dyspnea is still present two months later.
This patient manifested increasing cough and wheezing following an acute upper respiratory infection. On inhalation of penicillin aerosol the symptoms cleared and he left the hospital much improved. Roentgen-ray of the lungs before and after treatment showed no change. The improvement cannot definitely be ascribed to penicillin aerosol administration.
A case of acute lung abscess of five weeks' duration showed a large shadow of homogeneous density in the left hilar region in which the abscess cavity with a fluid level had become obscured. Inhalation of penicillin aerosol was promptly followed by decrease in temperature from an average of 102.5 to 100.2° F. A drop in respiratory rate from 26 to 20 and decrease in the white blood count from 25,000 to 16,000. No change in the area of pneumonitis by roentgen-ray was seen after treatment. Surgical drainage with recovery later.
Recurrent asthma for four years. Radical antral operation and vaccine therapy without benefit. For three weeks more cough and dyspnea. Improvement began with oral aminophylline and increased gradually with penicillin aerosol. Previous intramuscular injection of penicillin for eight days ineffective.

* The notes in this case were kindly submitted by Dr. E. P. Eglee, who used the nebulizer with a one liter volume.

latter route 60 per cent of the penicillin injected may be recovered from the urine. However, the percentage of penicillin found in the urine is an index of the amount absorbed rather than the effectiveness of aerosol administration. In infection of the pleural cavity penicillin by systemic injection is not curative, whereas local instillation may be followed by recovery. Similarly, in lung abscess the penetration of the aerosol into the cavity may be of special value in limiting the growth of organisms.

Clinical Results

The clinical results of 20 patients who inhaled penicillin aerosol are summarized in table 5. The length of treatment, except in two cases, was arbitrarily set at approximately five to 10 days. The aim of the study was to explore the early response of patients with various types of bronchopulmonary infection to penicillin aerosol therapy rather than to attempt a cure of the disease process. To what extent the method itself was practical, whether the drug in this form was irritating, the degree of elevation of blood level, the effect on the pathogenic sputum organisms—these questions were considered to require an answer before a sustained therapeutic trial of penicillin aerosol could be employed. The detailed case histories are, therefore, not presented but the significant data have been included in table 5.

There were five patients in whom inhalation of penicillin aerosol was followed by a marked improvement which appeared to be attributable specifically to the drug, i.e., three with bronchial asthma, one with lung abscess and one with bronchiectasis. In Case 3 an intractable form of asthma was relieved with a marked decrease in the signs of bronchial infection. The patient had previously required adrenalin by hypodermic injection every two to six hours most of the time over a period of nine years. For two months after treatment she had no asthma. The symptoms of cough and asthma then recurred, and a second course of treatment, at first with seven days of intramuscular injection and then six days of inhalation of penicillin resulted in no significant reduction in the number of injections of adrenalin employed, although the coughing was reduced and there was no wheezing between attacks. In Case 7 a striking improvement took place, manifested by decreased dyspnea and cough, and a marked clearing not only of sibilant but also the widespread moist râles which constituted good evidence for an infectious bronchiolitis. This improvement continued for two and one-half months when cough, dyspnea and wheezing gradually returned. A second course of penicillin aerosol resulted in progressive freedom from cough and asthma, clearing of both sibilant and moist râles and a truly remarkable clinical recovery in a patient unresponsive to routine measures. In Case 10 the inhalation of penicillin aerosol was accompanied by a striking clinical improvement although previous intramuscular injection of penicillin for one month had not appeared to be of significant value. The nature of the pneumonitis and questionable lung abscess was not determined. In

Case 12, a patient with bilateral bronchiectasis and intractable asthma resistant to adrenalin, there was a striking improvement after seven days' inhalation of penicillin aerosol. The patient remained free of asthma for one month when severe attacks began again. Inhalation of penicillin aerosol for 12 days resulted in no improvement. The response to penicillin aerosol in Case 17, treated for the first two days with 0.6 per cent neosynephrine-sulfathiazole and the last five days with penicillin aerosol, was surprising. Continuous dyspnea for five years, an end result of bronchiectasis and pulmonary fibrosis, was completely relieved. Respiratory graphic tracings showed a slight increase in maximal breathing capacity (increased tidal air) after inhalation of both 1 per cent epinephrine and 1 per cent neosynephrine, but no significant elevation of vital capacity. Bronchodilator drugs were, therefore, of little if any use. The diminution of the infection, and presumably the inflammatory swelling of the bronchial wall, was followed by the clearing of a previously incapacitating dyspnea. The fact that this improvement began with inhalation of a sulfonamide aerosol (neosynephrine-sulfathiazole) is of interest, since it indicates that this method deserves a wide trial in similar cases.[7b] At the present time, patients in this group continue chemotherapy with sulfonamide aerosols at home, either 2.5 per cent sulfadiazine (Pickrell's solution) or neosynephrine-sulfathiazole 1.5 c.c. being nebulized two to four times daily.

Summarizing the cases that responded very favorably, four patients with bronchial asthma were relieved of their symptoms for one to two months. Recurrence of attacks of asthma and cough was treated by a second course of penicillin aerosol without relief in two and complete relief in two patients. The patient with bronchiectasis and pulmonary fibrosis has remained remarkably free from dyspnea since treatment; she is inhaling a sulfonamide aerosol twice daily at home. The fifth patient with undiagnosed pneumonitis and questionable lung abscess remains well now three months after treatment.

Clinical improvement of moderate degree took place in 10 cases of bronchopulmonary disease but the nature of the illness was such as to prohibit a firm conclusion of the rôle exerted by penicillin aerosol. Of these, eight had bronchial asthma with bronchial infection, and in addition either pulmonary emphysema or bronchiectasis of some degree. Their course is summarized in table 5 (Cases 2, 4, 11, 13, 14, 15, 18, and 20). Recurrence of symptoms took place in four of eight of these improved cases within a period of approximately one month after five to eight days of inhalation of penicillin aerosol. Of the remaining three cases in this group one (Case 1) was that of lung abscess, and the roentgen-ray change in her case appeared to indicate a definitely favorable influence of penicillin administered through the lungs as compared to intramuscular injection. Another was a case of advanced bilateral bronchiectasis who was apparently temporarily improved (Case 16). Of the five remaining cases, one patient had a lung abscess with a closed cavity. Although the fever declined, there was no other significant

change in his clinical condition. Two long-standing cases of bronchiectasis with chronic lung abscess (Cases 8 and 9) and two cases of advanced pulmonary fibrosis were not significantly benefited. In no instance did the patient appear to be influenced adversely by penicillin aerosol therapy.

In addition to the adult group discussed above, five children with staphylococcus bronchitis, developing in association with congenital pancreatic deficiency, have been treated with inhalation of penicillin aerosol, for the most part by means of a catheter inserted in the oropharynx and more recently by inhalation with a mask rebreathing nebulizer apparatus. (These cases will be reported separately in detail by Dr. Dorothy H. Andersen.) Previous treatment of this type of disease by intramuscular injection of penicillin was tried on three patients in 1943 with temporary benefit only. Of the five cases treated by inhalation of penicillin aerosol with a dosage of 32,000 units per day for eight to 10 days, there was definite improvement in three patients. One patient, who was gravely ill with high fever, marked dyspnea and cyanosis, was dramatically improved after the inhalation of penicillin aerosol. The problem of technic of administration of aerosol to children is being studied at this time, and further trials of various methods are in progress. Culture of the nasopharynx showed a disappearance of *Staphylococcus aureus* in three patients tested before and after inhalation of penicillin aerosol.

Discussion

In appraising the value of administration of penicillin through the lungs a primary consideration is that of the safety of the method itself. Although the lungs of the 19 rats exposed to repeated inhalations of penicillin aerosol showed on microscopic section an increased incidence of scattered areas of congestion and edema, as compared to the lungs of the control animals, these changes were slight. Furthermore, the bronchi were entirely normal. The control animals were not treated with inhalation of normal saline and the possibility presents itself that such changes as were found may have been due to the fact that the animals were held with their heads in glass "helmets" and inhaled a considerable volume of fluid in the form of a nebulin. The differences between the two groups did not appear to be significant.

In 20 patients who were treated for seven days to one month there were four who manifested one or more of the following possible side-effects of the drug. Increased cough in one patient was noted at the end of a week of inhalation of penicillin aerosol. In three patients a sensation of substernal soreness was present for the better part of one day and then disappeared. The patient who had initially shown a decrease in peribronchial markings revealed at the end of one month of inhalation of penicillin aerosol a slight increase in peribronchial infiltration. The possible irritant effect of the drug may be considered as either slight, or negligible,

since the remaining patients in this series manifested nothing that could be interpreted as an irritant effect either clinically or by roentgen-ray before and after treatment. Furthermore, the seriousness of the clinical situation in the majority of patients treated would outweigh our questionable evidence for irritation as the result of inhalation of penicillin aerosol.

The fact that rats could be protected against an intraperitoneal injection of hemolytic streptococcus culture by inhalation of penicillin aerosol demonstrates that the drug is absorbed and therapeutically effective in combating systemic infection if an adequate dosage is administered. Since the heads of the rats were in a glass helmet and the penicillin aerosol was nebulized continuously by a flow of 4 liters per minute of oxygen, a considerable loss of the drug inevitably took place. In one group of four rats that were killed one-half hour after inhalation of 20,000 units of penicillin aerosol and whose blood was pooled for determination of the level of penicillin, 0.004 unit was found. Despite this minimal blood level approximately 50 per cent of rats may be protected by inhalation of penicillin as an aerosol.

The determination of the blood levels in the patients treated in this series revealed lower levels of penicillin than would be obtained by a comparable dosage administered intramuscularly. Higher blood levels can be obtained when the patients take a deep inhalation and hold the breath for several seconds. It may be observed that the mist of penicillin aerosol is not visible in the expired air under these circumstances, although it is readily seen if respiration is allowed to proceed normally. In the treatment of infection in the bronchial wall a local application of penicillin is the aim of treatment rather than a high blood level. However, deep inhalations and breath-holding are probably desirable even when the treatment of bronchial infection is intended. It may be ultimately discovered that a combination of penicillin injected intramuscularly, to provide a high blood level, and inhalation of penicillin aerosol will be the procedure of choice in patients with bronchiectasis or chronic bronchitis and bronchial asthma. In patients with lung abscess this may also prove to be the most effective procedure.

Since the penetration of penicillin aerosol into the abscess cavity is dependent upon its communication with a bronchus, deep inhalation would appear to be desirable in order to increase the lumen of the bronchi, and in that way facilitate entrance of penicillin into the cavity. Since it is known that injection of penicillin either intramuscularly or intravenously does not result in cure of empyema and that local instillation of the drug is often therapeutically successful, an argument can be made by analogy that local deposition of penicillin in a lung abscess may be of special value. The clinical response in the two cases that had previously received penicillin by intramuscular injection for one month offers merely suggestive evidence in this respect. However, one of these patients appeared gravely ill with severe dyspnea in an oxygen tent at the time penicillin aerosol administration was commenced. A week later the patient's temperature had decreased

from 103° F. to 100° F., and there was coincident striking clinical improvement. This apparent response to inhalation of penicillin aerosol justifies the suggestion that this procedure be tried in other cases of acute lung abscess either in conjunction with or without intramuscular injection of penicillin.

Although the immediate response to inhalation of penicillin aerosol revealed the disappearance of the predominating organisms in the sputum culture, further evidence is needed concerning the duration of absence of pathogenic organisms. In all likelihood a longer period of treatment will be required to overcome chronic infection in the bronchial wall. The recurrence of symptoms in three of five patients who were strikingly improved and four of eight who appeared moderately improved offers the opportunity of testing the effectiveness of the procedure itself. In two patients a second course of treatment was completely successful. The duration of treatment as well as the most efficient form of proceeding in administration of penicillin in cases of this type requires further investigation. The apparatus for automatic delivery of penicillin during the inspiratory cycle is now being tried clinically.

Additional studies are needed to determine the optimum dosage. It has been shown that it is clinically feasible to administer 40,000 to 50,000 units of penicillin in 1 c.c. of normal saline, four to five times daily. The nebulizer made by the Vaponefrin Company and the No. 40 type of the DeVilbiss Company produce particles that are mostly smaller than 1 micron in diameter. Particles of this size penetrate into the lungs and are less apt to be deposited on the tracheobronchial tree than those of larger size. It may ultimately be found that a range of particle size somewhat larger than that produced in this type of nebulizer may be an advantage. However, the fact that larger particles may be lodged on the larynx and trachea would be a disadvantage since they would contain the major portion of penicillin. (The plastic nebulizers made by the Vaponefrin Company and the Nephron Company appear to be the best of this type.) The addition of a large bulb of 1000 c.c. capacity attached to the upper surface of the Vaponefrin nebulizer has the function of serving as a reservoir for some of the exhaled air which contains a moderate amount of penicillin in ordinary breathing.

The maintenance of a blood level as high as 0.4 unit as a result of deep breathing was shown in the patient who inhaled 100,000 units in 1 c.c. If a high blood level were desired in emergency situations in which repeated intramuscular injections were not feasible, the procedure of inhalational absorption of penicillin could be carried out. Although the method is not to be considered as a potential replacement of systemic administration of this drug, situations may occur in which the inability to secure either a doctor or a nurse for injection of penicillin might be handled by administration of penicillin aerosol in relatively large doses. Since the dosage for

injection of penicillin intramuscularly has been well established, it should be given in this way whenever it is possible to do so.

Summary and Conclusions

The inhalation of penicillin aerosol as a clinical therapeutic procedure was studied from various points of view.

In respect to its possible irritant effect on the lungs, in concentrations between 5,000 to 50,000 units per c.c., the lungs of 19 rats, exposed to repeated inhalations of the drug, were compared to those of control animals. The differences on microscopic section were not considered significant, although the incidence of congestion and other changes was slightly greater in the treated animals. Administration of penicillin aerosol to 20 patients for seven days to one month offered no convincing evidence of an irritant effect on the lungs. A sensation of substernal soreness was experienced by three patients for one day or less. Inhalations of 20,000 to 100,000 units per c.c. in 10 normal and miscellaneous controls did not result in a subjectively perceived irritant effect.

Rats were protected against intraperitoneal injection of hemolytic streptococcus culture by a single inhalation of 25,000 units of penicillin aerosol. The head of the rat was enclosed in a glass helmet into which a continuous stream of aerosol was delivered.

In human subjects the penicillin solution was aerosolized by the passage of 5 to 8 liters per minute of oxygen through a nebulizer containing 1 c.c. of penicillin in concentrations between 20,000 and 100,000 units per c.c. By means of a Y tube between the oxygen regulator and the nebulizer, the penicillin was aerosolized only during the inspiratory cycle. When a 1000 c.c. glass bulb is fused to the upper surface of the nebulizer some of the penicillin in the exhaled air is re-inhaled. This modification is not essential but permits a greater economy in the use of the drug than the standard nebulizer. An apparatus which provides penicillin aerosol during the inspiratory cycle only without the need of the patient's coöperation is being tried at this time.

An exploratory study of the effectiveness of penicillin aerosol therapy in 20 patients with bronchopulmonary infection revealed: (1) the predominating organisms in the sputum culture were consistently absent 24 hours after discontinuance of treatment; (2) the blood level of penicillin for one hour following inhalation of the aerosol was generally between 0.01 and 0.04 unit, at times as high as 0.18. In a patient without pulmonary pathology, in whom deep breaths were taken during the inhalation of 100,000 units in 1 c.c., a blood level of 0.4 was present for one hour; in this patient 20 per cent of the inhaled penicillin was recovered in the urine. The aim of treatment, however, is generally not a high blood level but a local application of penicillin on the bronchial wall.

The results are to be considered in the light of an arbitrarily imposed

limit of treatment, as well as a varied pathology. The 20 cases treated suffered from (a) varying combinations of bronchial asthma, bronchiectasis, and pulmonary emphysema; (b) bronchiectasis with and without chronic lung abscess; (c) pulmonary fibrosis and emphysema; (d) acute lung abscess. In five patients the improvement was marked and seemed definitely the effect of inhalation of penicillin aerosol. In 10 others improvement was moderate, and in the remaining five cases no significant clinical benefit was achieved. Of the 15 improved cases, seven suffered a recurrence of symptoms in two months or less. Further studies on the effect of penicillin aerosol are indicated in (a) bronchial asthma with bronchial infection; (b) bronchiectasis; and (c) acute lung abscess.

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PENICILLIN THERAPY AT THE UNIVERSITY OF MINNESOTA HOSPITALS: 1942–1944 *

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On July 9, 1942, J. E., a seven year old girl, entered the University Hospitals. Two days later, she received penicillin because of a severe staphylococcic bacteremia, with 68 colonies of coagulase-positive staphylococci per cubic centimeter of blood. Pneumonia and an acute osteomyelitis of the left femur were also present. Her general condition improved rapidly. This patient was the first to receive penicillin at the University Hospitals. Since that time, over a period of two years, a total of 200 patients have received penicillin under our supervision. The purpose of this report is not to review the voluminous literature on penicillin, but to present the types of infections treated, the results of therapy, and to discuss briefly some of the clinical problems relating to this new chemotherapeutic agent. Although a majority of the patients were treated at the University Hospitals, several important types of infections were treated in other institutions through the coöperation of physicians in Minneapolis and St. Paul. This applies particularly to a group of infants and children treated at the Abbott Hospital in Minneapolis with the aid of Dr. Georgie M. Burt, Resident in Pediatrics.

In every instance an attempt was made to isolate the etiological agent from the local lesions or the body fluids before treatment was undertaken. Dr. Gerald Needham, Head of the Bacteriological Laboratories at the University Hospitals, was most helpful in this respect. The types of infections treated during a period of two years are summarized in table 1.

One hundred and ninety of the patients received the sodium salt of penicillin, and 10 had the calcium salt administered to them. There did not appear to be any essential difference in the therapeutic response of the patients to either one of the salts. The material was injected parenterally, and in a few instances, applied locally to infected wounds or burns. When administered parenterally, the intravenous or intramuscular routes were employed. None was given subcutaneously. The material was dissolved in sterile physiological saline solution and given as an intravenous drip, or as

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TABLE I

Summary of Types of Infections Treated with Penicillin

	No. of Cases
Staphylococcic Infections	
Staphylococcic bacteremia without osteomyelitis	20
Staphylococcic bacteremia with osteomyelitis or suppurative arthritis	8
Acute staphylococcic osteomyelitis or suppurative arthritis without demonstrable bacteremia	3
Chronic staphylococcic osteomyelitis without demonstrable bacteremia	13
Staphylococcic infections without demonstrable bacteremia	13
Streptococcic Infections	
Hemolytic streptococcic bacteremia	7
Streptococcic infections without demonstrable bacteremia	12
Meningitis	
Pneumococcic	14
Meningococcic	10
Staphylococcic	3
Pulmonary Infections	
Pneumococcic pneumonia without empyema	9
Non-pneumococcic pneumonia without empyema	11
Empyema	10
Subacute Bacterial Endocarditis and Endarteritis	10
Sulfonamide Resistant Gonorrhea	16
Gonorrhea with Arthritis	4
Genitourinary Tract Infections	22
Miscellaneous Infections	15
	200

intermittent intravenous or intramuscular injections. In a few instances, the penicillin was dissolved in sterile distilled water with 5 per cent dextrose. The local application was made with saline solutions of penicillin containing 250 to 500 units per cubic centimeter or with an ointment having 500 units per gram.

RESULTS OF TREATMENT

Staphylococcic Infections

Fifty-seven patients had infections due to staphylococci. It is significant that in recent years more cases of staphylococcic sepsis have been seen at the University Hospitals than instances of streptococcic disease. This probably is due in part, at least, to the fact that physicians throughout the State have succeeded in controlling many streptococcic infections with sulfonamide therapy. On the other hand, as is generally agreed, the sulfonamides are not so effective in the treatment of staphylococcic infections. For purposes of a more critical analysis, the cases of staphylococcic sepsis have been divided into several groups.

Staphylococcic Bacteremia With and Without Osteomyelitis. Cases of staphylococcic bacteremia without primary or metastatic bone lesions have been separated from those having osteomyelitis or suppurative arthritis be-

cause in our experience and those of others the mortality rate of the former group has been shown to be definitely higher than in those with osseous complications. It is generally accepted that the mortality rate of untreated cases of staphylococcic bacteremia varies between 61 and 91.4 per cent. There is considerable evidence that the use of the sulfonamides, particularly sulfathiazole, has reduced this mortality rate in recent years, but the results, in general, have not been satisfactory.

Twenty patients having bacteremia without osteomyelitis due to coagulase-positive staphylococci were treated with penicillin. Of this group, 13 recovered and seven died, giving a mortality rate of 35 per cent as noted in table 2. An analysis of the fatal cases indicates that three patients received inadequate doses of penicillin; two patients had an acute staphylococcic endocarditis; and two patients received what is considered to be sufficient penicillin but a bacteremia was still present at the time of death. Of the patients who recovered, there were four infants under 12 months of age. The youngest patient was 12 days old. In general, the therapeutic results with the entire group were considered to be more satisfactory than those obtained with the sulfonamides.

TABLE II

Acute Staphylococcic Bacteremia:
Results in 28 Patients Treated with Penicillin

	No. of Cases	Recovered	Died	Mortality Rate
Without osteomyelitis or arthritis.....	20	13	7	35%
With osteomyelitis or arthritis.....	8	7	1	12.5%

Of the eight patients having staphylococcic bacteremia with osteomyelitis or suppurative arthritis, seven recovered. The one fatal outcome occurred in an individual with an acute staphylococcic endocarditis of the mitral valve. The results of treatment with penicillin upon the bone lesions will be discussed shortly.

Although varying doses of penicillin were used in the 28 patients having bacteremia, a general statement concerning dosage schedules may be made. In the present investigation, the purpose has been to clear the blood stream of organisms as soon as possible, and also to sterilize any primary or metastatic foci. In the zeal to accomplish these ends, larger doses than the minimal requirements may have been used. There still exists divided opinion among reliable investigators concerning optimal doses. Our policy is to use large initial doses, preferably by means of an intravenous drip, and then to give subsequent smaller doses intermittently by the intramuscular route.

Doses of Penicillin for Infants. An initial dose of 10,000 units may be given in an intravenous drip using 150 c.c. of physiological saline solution. As much as 25,000 units have been given in this manner. Because of the

difficulties often associated with administering intravenous solutions to infants, a practical and successful method of giving penicillin is to inject 5,000 units of penicillin contained in 0.5 c.c. saline solution intramuscularly every two to three hours until the infection is brought under control. Then 2,000 to 2,500 units may be given intramuscularly every three hours until the temperature remains normal. The maximal total dose was used in an infant 12 days old, and amounted to 755,000 units given over a period of 20 days.

Doses of Penicillin for Adults. The procedure, used with satisfactory results, has been that of injecting 20,000 units intramuscularly every two hours for at least the first 24 hours, and then 10,000 to 15,000 units every three hours thereafter until the infection has been brought under control. Patients seriously ill and often dehydrated have been given 50,000 to 100,000 units as an intravenous drip over a period of 10 to 12 hours, utilizing a liter of physiological saline solution for this purpose. This dose has been repeated every 10 to 12 hours for several doses. After initial doses of this magnitude, 15,000 to 20,000 units have been given intramuscularly every three hours until the temperature has remained normal or the infection has been brought under control. The total dose employed has approximated one million units. Obviously, any foci should be drained surgically when indicated. In patients having bacteremia associated with osteomyelitis, the schedule of doses used has been approximately the same as employed for bacteremia without osteomyelitis except therapy was continued for a longer period of time resulting in a larger total dose of penicillin. The patients with osseous lesions received between two and three million units of penicillin.

Acute and Chronic Staphylococcic Osteomyelitis or Suppurative Arthritis. The therapeutic results with 24 patients who received penicillin are shown in table 3. Twenty-two of these patients had osteomyelitis of the long

TABLE III

Staphylococcic Osteomyelitis or Arthritis:
Results in 24 Patients Treated with Penicillin

	No. of Cases	Improvement	Complete Recovery	No Improvement
Acute osteomyelitis	8	4	3	1
Acute suppurative arthritis	3		3	
Chronic osteomyelitis	13	8	2	3

bones; one had osteomyelitis of the ribs; and three had an acute suppurative arthritis.

Six of the eight patients with acute osteomyelitis had a demonstrable staphylococcic bacteremia. As already stated with reference to table 2, one of these patients died because of acute staphylococcic endocarditis. Of the remaining five patients having acute osteomyelitis with bacteremia, only

one, a three year old child, has had a complete recovery. In this instance, a recent roentgenogram of the left femur shows evidence of considerable bone destruction and new bone formation. In four patients signs of active osteomyelitis persisted after therapy had been discontinued.

Three patients who had acute staphylococcic arthritis had no evidence of infection after the completion of therapy. Two had an early suppurative process of the hip and bacteremia, and recovered completely. One case of suppurative arthritis of the right elbow recovered with a residual limitation of motion of the joint after 1,415,000 units of penicillin had been administered.

Two patients having acute osteomyelitis without bacteremia recovered completely. One of these individuals had a lesion of the neck of the right femur, and seven months after receiving 1,260,000 units of penicillin in 18 days, there is no evidence of a residual infection. The second case had a suppurative pericarditis and empyema in addition to osteomyelitis of the right tibia. Fifteen months after receiving 1,195,000 units of penicillin, there are no signs of bone infection.

Thirteen cases of chronic osteomyelitis have received penicillin. Two of the patients apparently have recovered completely; eight patients had temporary improvement; and three persons showed no improvement.

In summarizing the results of therapy with penicillin in a small series of cases, it may be stated that complete recovery was effected in less than one half the cases of acute osteomyelitis. Although clinical improvement occurred in the remaining cases, staphylococci have been cultured from draining lesions months after the completion of treatment. The results with chronic osteomyelitis revealed that only two of 13 patients have recovered completely from their infection. It is possible that a total dose of two to three million units of penicillin is inadequate for the treatment of osteomyelitis. It appears quite likely that surgical intervention in conjunction with penicillin therapy will yield better results, particularly in the treatment of chronic osteomyelitis of the long bones. More recently, another therapeutic attack against chronic osteomyelitis is being evaluated in coöperation with Dr. Clarence Dennis of the Division of Surgery. A total of one to two million units of penicillin is being administered parenterally. Then surgical removal of any sequestrum is carried out, and the infected bone is saucerized. If in vitro tests reveal that the offending strain of staphylococcus is sensitive to sulfathiazole, crystals of this compound are placed in the saucerized bone before closing the wound. Penicillin is then administered postoperatively for a total of one to two million units.

Staphylococcic Infections Without Demonstrable Bacteremia. Sulfonamide therapy had been used in this group of 13 patients, prior to the administration of penicillin. There were four individuals with suppurative otitis media and mastoiditis. Two children in this group recovered completely in a short period of time after receiving 205,000 and 525,000 units of penicillin. In two adults, it was necessary to perform mastoidectomies before

TABLE IV

Staphylococcic Infections without Bacteremia:
Results in 13 Patients Treated with Penicillin

	No. of Cases	Improvement	Complete Recovery	No Improvement
Otitis media and mastoiditis	4	2	2	
Sinusitis	1	1		
Soft tissue infections	8	2	2	4

the infections were completely eradicated. One infant with staphylococcic sinusitis exhibited improvement, but not complete recovery, after receiving 475,000 units.

The remaining eight patients had infections of the soft tissues. Penicillin was applied directly to the lesions in five of the eight patients. One patient with extensive third degree burns failed to improve, and a second individual with multiple subcutaneous abscesses had only temporary improvement. In the other three patients, local therapy was combined with parenteral treatment, followed by slight to definite improvement. Of the remaining three patients, one recovered completely from a bilateral orbital cellulitis; one diabetic adult with multiple subcutaneous abscesses recovered completely; whereas a third individual with an abscess of the thigh failed to respond to penicillin.

Streptococcic Infections

Hemolytic Streptococcic Bacteremia. Like staphylococcic bacteremia, the mortality rate of untreated patients with bacteremia due to hemolytic streptococci is over 70 per cent, but unlike staphylococcic bacteremia, the sulfonamide compounds have decidedly reduced this mortality rate. As shown in table 5, seven patients with hemolytic streptococcic bacteremia were treated

TABLE V

Streptococcic Infections:
Results in 19 Patients Treated with Penicillin

	No. of Cases	Complete Recovery	Improvement	No Improvement	Died
Hemolytic streptococcic bacteremia	7	3			4
Hemolytic streptococcic soft tissue infections	2	2			
Streptococcic sinusitis	3	2	1		
Streptococcic otitis media	3	3			
Streptococcic otitis media with mastoiditis	4	1	3		

with penicillin. Three of the patients recovered, and four died, but an analysis of the fatal cases revealed that in every instance the blood stream was rapidly cleared of organisms, and death was attributed to other factors. One patient died because of an aplastic anemia; one had acute lymphatic leukemia;

a third fatality was due to a pulmonary embolism; and the fourth patient apparently recovered from a severe streptococcic bacteremia, and died several days later from causes which were not clearly established even after a complete postmortem examination.

The doses of penicillin required for the treatment of streptococcic bacteremia were less than those used in patients with staphylococcic bacteremia. This may be related to the fact that most strains of hemolytic streptococci are more sensitive to the antibacterial action of penicillin than are staphylococci. Usually, the bacteremia may be eradicated by giving 20,000 units intramuscularly every two to three hours for 24 hours, and then 10,000 to 15,000 units every three hours for a few days thereafter. The total dose required will depend upon the nature of the primary or metastatic lesions, and whether they are amenable to surgical drainage. The maximum dose used was one million units.

Streptococcic Infections Without Demonstrable Bacteremia. Twelve patients are included in this group, three of them having infections due to non-hemolytic streptococci. Two individuals had chronic lesions of the soft tissues which had been treated with the sulfonamides. Rapid recovery followed the parenteral use of penicillin. Two patients had a severe and acute sinusitis with osteomyelitis of the frontal bones due to hemolytic streptococci. Complete recovery followed therapy with penicillin. One patient had an acute sinusitis with orbital abscesses due to non-hemolytic streptococci. Recovery was gradual but complete after the use of over one million units of penicillin. Three patients had a suppurative otitis media, and observation of these cases indicates that treatment with penicillin is associated with rapid and complete recovery. Four patients had a suppurative otitis media with mastoiditis. Treatment with penicillin was followed by complete recovery in one instance. The other three patients improved, but mastoidectomies were necessary. The doses of penicillin used in all of the foregoing cases were essentially the same as used in the treatment of the patients with bacteremia.

It would appear from clinical observations and in vitro tests that some strains of non-hemolytic streptococci are more resistant to penicillin than the Lancefield group A hemolytic streptococci.

In connection with hemolytic streptococcic diseases it should be pointed out that *after* the establishment of an infection the administration of penicillin will not prevent the development of acute rheumatic fever. Furthermore, therapy with penicillin is contraindicated as specific treatment for acute rheumatic fever.

Meningitis

A total of 27 patients with bacterial meningitis have been treated with penicillin. The types of meningitis and the results of therapy are shown in table 6.

TABLE VI
Meningitis:
Results in 27 Patients Treated with Penicillin

	No. of Cases	Recovered	Died	Mortality Rate
Meningococcic	10	9	1	10%
Pneumococcic	14	11	3	21%
Staphylococcic	3	2	1	33⅓%

Pneumococcic Meningitis. This is a serious form of meningitis with a uniformly fatal outcome in untreated cases. Even with the use of the sulfonamides and type specific antipneumococcic serums mortality rates ranging from 60 to 80 per cent have been reported. It would appear that these rates may be reduced considerably following the administration of penicillin. Fourteen patients have received penicillin followed by 11 recoveries. This yields a mortality rate of 21 per cent. If the death of one patient is discounted because penicillin was not injected intrathecally, the mortality rate in the remaining 13 individuals is 15 per cent. Operative procedures carried out in this group include mastoidectomy in three patients, and myringotomy in four. Although sulfonamide therapy was employed concurrently in several patients, it is difficult to assay the value of this procedure. Five infants under 12 months of age were treated and all recovered. Of the three fatal cases, one died because of acute heart failure due to an acute aortic endocarditis with rupture of an aortic cusp, but without evidence of meningitis. The other two fatal cases were due to meningitis.

In small infants, the dose of penicillin was 2,500 to 5,000 units intramuscularly every three hours, and 2,000 to 5,000 units of penicillin in 5 c.c. of physiological saline solution injected intrathecally every 12 to 24 hours. The total dose used was from 300,000 to 500,000 units. For adults, initial doses of 50,000 to 75,000 units of penicillin were given intravenously as a continuous drip for 12 hours in one liter of physiological saline solution. This was repeated for two to three doses in several instances. Then the patients were given 10,000 to 15,000 units intramuscularly every three hours. From 10,000 to 15,000 units in 10 c.c. of physiological saline solution were injected intrathecally every 12 to 24 hours until the fluid became sterile and clear. In a few instances, the penicillin was injected directly into the cisterna magna. The total dose of penicillin approximated one million or less units.

Meningococcic Meningitis. Although this type of meningitis generally responds quite satisfactorily to sulfonamide therapy, a group of unusually severe cases was seen and treated in coöperation with the Staff of the Division of Neuropsychiatry at the University Hospitals. Dr. A. B. Baker classified some of the patients as having meningo-encephalitis due to the meningococcus. Sulfonamides had been employed without entirely satisfactory results, and, therefore, penicillin was administered. Ten cases were

treated and nine patients recovered. One adult with a block in the intrathecal space failed to respond and died. The same routine was used in treating these patients as detailed for the therapy of pneumococcic meningitis with the exception that the total dose of penicillin was approximately 50 to 75 per cent of that used for pneumococcic meningitis, and the total number of intrathecal injections was less.

Staphylococcic Meningitis. Three infants were treated and two recovered. One infant, three weeks of age, received a total of 199,000 units in 20 days, in doses of 1,000 units intramuscularly every three hours, and 2,000 units intrathecally daily for 19 days. A second infant, two months old, received 1,096,500 units in 54 days with 3,000 units given intramuscularly every three hours and 3,000 units injected intrathecally every 12 hours. Both of these patients recovered but during therapy developed epidural abscesses at the site of the intrathecal injections. This complication was cured by injecting penicillin directly into the abscesses. A third infant with a meningo-myelocele died with a meningitis due to *E. coli* and staphylococci. Sulfadiazine was also administered. Staphylococci disappeared from the cerebrospinal fluid but the *E. coli* persisted.

Pulmonary Infections

Penicillin has proved to be highly effective in the treatment of certain types of infections involving the respiratory tract and pleural cavities. Thirty patients are included in this group of patients. For purposes of discussion, the cases are divided into four groups as given in table 7.

TABLE VII

Pulmonary Infections:
Results in 30 Patients Treated with Penicillin

	No. of Cases	Complete Recovery	Improvement	No Improvement	Died
Bacterial pneumonia (non-pneumococcic)	9	4	3	1	1
Non-putrid lung abscess	2	2			
Pneumococcic pneumonia	9	5			4
Empyema	10	8	1		1

Bacterial Pneumonia (Non-pneumococcic). Nine patients, who had evidence of a bacterial type of pneumonia but not proved to be pneumococcic in origin, were treated. One of the nine patients died. In this case, Gram positive diplococci were recovered from the sputum, but routine typing with antipneumococcic sera failed to show a specific reaction. The patient did not respond to penicillin, and postmortem examination revealed an acute endocarditis of the aortic valve. Three other patients, with similar bacteriological data, recovered. One patient with a mixed flora of bacteria in the sputum, failed to improve, and subsequently, bilateral pulmonary tuberculosis was shown to be present. Of four cases with staphylococcic pneu-

monia, three recovered completely and one was markedly improved following treatment with penicillin. One patient having an involvement of all five lobes due to non-hemolytic and hemolytic streptococci failed to improve with penicillin, but concurrent therapy with sulfamerazine resulted in a slow and complete recovery. One patient with staphylococci and non-hemolytic streptococci in the sputum improved slowly.

The schedule of doses used in the foregoing patients was essentially the same as employed for individuals with pneumococcic pneumonia, except that the total doses were greater.

Non-putrid Lung Abscesses. Two patients were treated successfully. Both had previously received sulfonamides without improvement. One adult had multiple pulmonary abscesses due to staphylococci, bilateral pleural effusion, and possibly a brain abscess. After receiving 2,452,000 units of penicillin over a period of 33 days, he recovered completely. A second patient had a large pulmonary abscess with non-hemolytic and hemolytic streptococci, and coagulase-positive staphylococci in the sputum. After one course of penicillin totalling 1,205,000 units and given in 22 days, he was markedly improved. A relapse ensued, however, and an additional 1,795,000 units were injected over a period of 40 days. This patient recovered completely.

It would appear that in the treatment of the less acute cases of pulmonary suppuration with penicillin it may be necessary to treat such patients for several weeks.

Pneumococcic Pneumonia. The mortality rate of pneumococcic pneumonia has been markedly reduced as a result of sulfonamide therapy. It would appear that all types of pneumococci are sensitive to penicillin. Although physicians may still obtain satisfactory clinical results with the sulfonamides, penicillin is indicated for use in those patients not responding to a sulfonamide. On the other hand, as our data with a small group of patients illustrate, fatalities may be anticipated even with penicillin available. It is apparent that the indications for the use of specific antipneumococcic serum in the treatment of pneumococcic pneumonia are growing less and less.

In the present series of cases, nine patients with pneumococcic pneumonia, four of whom had demonstrable bacteremia, were treated with penicillin, and five patients recovered. Of the fatal cases, one showed no improvement, having a persistent bacteremia, and death was presumably due to acute pneumococcic endocarditis. A second patient apparently had recovered from pneumonia and death was ascribed as being due to ventricular fibrillation. A third patient with a pneumonia due to type XXXIII pneumococci failed to respond and died because of a complicating diabetic acidosis and nephrosis. A fourth patient with a postoperative pneumococcic pneumonia improved, but died as a result of a splenectomy.

Relatively small total doses of penicillin suffice for the treatment of pneumococcic pneumonia. Satisfactory results have been obtained with

500,000 units. Fifteen thousand to 20,000 units given intramuscularly every two to three hours will usually cause a drop in temperature and clinical improvement within the first 24 hours. Subsequent treatment calls for 10,000 units every three hours for two or three days. Patients with pneumococcic pneumonia often require parenteral fluids, and penicillin may be given intravenously in the form of a continuous drip utilizing 50,000 units in a liter of physiological saline solution.

Empyema. Suppuration of the pleura due to pyogenic cocci has not responded very satisfactorily to sulfonamide therapy. In many instances, surgical drainage of the pleural cavities has been necessary. The results in 10 patients would indicate that more satisfactory responses will be forthcoming with penicillin. There were six patients who had coagulase-positive staphylococci in the purulent empyema fluid. In five of the six patients, the infection was controlled and complete recovery effected following the introduction of penicillin directly into the pleural spaces. The sixth patient had an infection due to staphylococcus, type XX pneumococcus and *Aerobacter aerogenes.* Penicillin succeeded in eradicating the pneumococci and staphylococci, but the *Aerobacter aerogenes* persisted in the aspirated material. Open drainage of the pleural cavity was necessary, but the patient eventually died because of an aspiration pneumonia. In the treatment of staphylococcic empyema, the total amount of penicillin to be employed, the quantity to be injected intrapleurally, and the question of simultaneous parenteral penicillin therapy depend upon the age of the patient, the size of the empyema cavity, and the clinical condition of the patient. Thus in an infant three weeks old with a right pyopneumothorax, a total dose of 97,250 units was used. Three thousand units were placed in the pleural cavity every 24 to 48 hours, and the material was also administered parenterally. The patient recovered completely. In adults, from 10,000 to 100,000 units in up to 200 c.c. of physiological saline solution have been introduced intrapleurally every day. Prior to each injection, as much of the fluid as possible was removed with a needle and syringe. It was surprising in some instances how long the empyema fluid continued to contain staphylococci, and only persistent treatment finally brought the infection under control. In most instances, penicillin was also administered parenterally in doses of 10,000 to 15,000 units every three hours because of the patient's general condition. The total amount of penicillin used in the treatment of staphylococcic empyema was approximately one million units.

One patient with an empyema due to streptococci of the viridans type improved with sterilization of the empyema fluid, but open drainage was necessary to close the cavity. Another patient having empyema due to a non-hemolytic streptococcus recovered completely. This also applies to an empyema due to type I pneumococci. Another patient with an encapsulated mediastinal empyema due to hemolytic streptococci recovered almost dramatically after 100,000 units of penicillin were injected intrapleurally on two occasions.

Subacute Bacterial Endocarditis or Endarteritis

Subacute bacterial endocarditis is practically a uniformly fatal disease, and only rarely has therapy with the sulfonamides provoked a remission. Surgical intervention in cases of patent ductus arteriosus with subacute bacterial endarteritis has been followed by complete remissions and probable cures. Apparently a more hopeful outlook may be anticipated in patients with subacute bacterial endocarditis following the continuous administration of large doses of penicillin. Even here, however, a reasonable lapse of time is necessary before final conclusions may be drawn. Eight cases of subacute bacterial endocarditis and two cases of patent ductus arteriosus associated with bacterial endarteritis have been treated with penicillin at the University Hospitals. Heparin has not been employed as an ancillary therapeutic agent. We cannot subscribe to the use of heparin or any other anticoagulant in patients with bacterial endocarditis. A fatal cerebral hemorrhage was induced in two patients when sulfapyridine was administered along with heparin.

Of the eight patients having subacute bacterial endocarditis, each of four individuals received less than one million units of penicillin without benefit. The four remaining patients received 4,200,000 units given in doses of 120,000 units every 12 hours as a continuous intravenous drip. The penicillin was dissolved in either one liter of physiological saline solution or one liter of sterile distilled water containing 5 per cent dextrose. One patient was not improved and an autopsy revealed bacterial vegetations with ulceration of both the aortic and mitral valves. A second patient had a remission in fever and blood cultures remained sterile, but death at the conclusion of therapy was due to peritonitis following rupture of a huge abscess of the spleen. A large vegetation on the mitral valve contained viable *Streptococcus viridans*. A third patient appeared to be in complete remission but his cardiac reserve was very low and he died five weeks after the completion of therapy because of heart failure. There was only a small vegetation a few millimeters in size on an aortic leaflet but a rupture of a chorda tendineae had taken place because of a small ulcerative vegetation. However, *Streptococcus viridans* was recovered from the vegetations. A fourth patient had a remission for four weeks following the completion of treatment. At the end of this period he had a relapse with bacteremia, fever, and embolic phenomena.

One patient had a ligation of a patent ductus arteriosus. Two months following operation the murmur reoccurred, probably due to recanalization, and the signs of acute bacterial endarteritis appeared. He was given 3,000,000 units of penicillin and all signs of the infection have been absent for four months. A second patient with patent ductus arteriosus and endarteritis had 225 colonies of *Streptococcus viridans* per cubic centimeter in her blood stream. She received 4,200,000 units with a complete subsidence of all signs of her infection. Following this treatment the ductus was sev-

ered and ligated. The improvement in this young adult's general condition has been extremely satisfactory.

Before patients are treated with penicillin, in vitro tests are carried out with a standard inoculum of the causative organisms to detect the sensitivity of the strains to penicillin. It would appear that more desirable results will be obtained if complete inhibition of growth is obtained with penicillin in concentrations that may be readily attained and maintained in human beings.

Gonococcic Infections

Sulfonamide-Resistant Gonorrhea. Sixteen patients, 13 males and three females, having gonorrhea for one to 30 weeks have been treated successfully with penicillin. The total amount of penicillin used varied between 75,000 to 270,000 units, an average of 100,000 units being given in doses of 20,000 units intramuscularly every two to three hours for five doses. One patient, having an acute epididymitis as a complication, was at first thought to have been completely under control following 150,000 units, but he had an exacerbation of epididymitis after physical activity. Another 120,000 units was necessary before the inflammatory process subsided. At the present time, at least, we believe that patients having acute gonorrhea should be hospitalized for therapy with penicillin. Whether short cuts in therapy are possible so that an individual may be treated in a physician's office with smaller doses, or with less frequent injections must be investigated carefully. A potential danger lurks in such a procedure in that patients may be inadequately treated, and strains of gonococci resistant to penicillin may be developed and disseminated. This has been the history of sulfonamide therapy.

Gonococcic Arthritis. Four patients with gonorrhea and acute arthritis were treated with the total doses of penicillin varying between 100,000 and 707,500 units. Although the gonorrhea was readily controlled, joint tenderness and pain persisted for several days after the conclusion of therapy. This is understandable when one considers the nature of gonococcic arthritis. Within a relatively short period of time after the onset there is an inflammatory reaction of the synovial membrane, and, in some instances, a destruction of joint cartilage. Even following the eradication of viable gonococci this inflammatory reaction subsides slowly. If penicillin could be given parenterally very shortly after the onset of arthritis, and also injected directly into the larger joint spaces when indicated the response might be more dramatic. In our patients, the arthritis was of several days' duration, and the smaller joints of the wrist and feet were involved.

Genitourinary Tract Infections

Of the 22 patients, 16 constitute a group who have been investigated in coöperation with Dr. C. D. Creevy, Head of the Division of Urology at the University Hospitals. All of them were males with benign prostatic

hypertrophy on whom transurethral resection of the prostate gland was carried out. Relatively small doses of penicillin were administered parenterally shortly before and after operation in an attempt to control a bacteremia or local infection, which are not uncommon complications of this type of surgery. Obviously, conclusions can only be drawn after a larger group is treated.

Four patients having pyelonephritis were treated. They were given 300,000 to 500,000 units of penicillin. Two improved, one recovered completely, and the fourth showed no improvement. Two remaining patients had chronic cystitis. One had temporary improvement, whereas the other failed to improve. All of these patients had infections associated with pyogenic Gram positive cocci. All had received prior sulfonamide therapy. More information is necessary before recommendations can be made concerning the value of penicillin in the treatment of genitourinary tract infections.

Miscellaneous Infections

Fifteen patients with miscellaneous infections were treated.

Peritonitis. There were four patients in this group. All had generalized peritonitis. Two followed perforation of a hollow viscus; one followed a colectomy; and a third resulted from a ruptured appendix. Two recovered. Although one cannot draw conclusions from four cases, one is probably justified in using penicillin in the therapy of peritonitis. Since a mixed type of bacterial flora is usually involved, it may be necessary to supplement penicillin with one of the sulfonamides. It would appear that relatively large doses of penicillin may be necessary.

Dermatological Lesions. One patient with generalized pemphigus was treated. Hemolytic streptococci, staphylococci and proteus bacilli were isolated from the bullae. No improvement followed the use of large doses of penicillin. A similar result was obtained in a second patient with a chronic dissecting pyoderma. A third patient with severe acne conglobata and a bacteremia due to unidentified Gram positive cocci improved following therapy with penicillin. No new skin lesions developed while the patient was under observation.

Pneumococcic Bacteremia Without Pneumonia. Two patients were treated. One recovered. A fatal outcome in the second patient was associated with an acute ulcerative endocarditis due to type XXII pneumococci.

Chronic Burrowing Undermining Ulcer ("Meleney Ulcer"). One patient with a large dissecting lesion of the abdominal wall due to microaerophilic hemolytic streptococci was improved but temporarily following the local and parenteral employment of large doses of penicillin.

Gas Gangrene. One patient, critically ill with a bacillemia following amputation of a lower extremity for gas gangrene, recovered following the use of large parenteral and local doses of penicillin.

Actinomycosis. One patient with abdominal and rectal fistulae due to actinomycosis improved considerably following the parenteral administration of two million units of penicillin. However, actinomyces were still recovered from the abdominal drainage at the conclusion of therapy.

Localized Intra-abdominal Infections. One patient with a postoperative subphrenic abscess improved coincident with the administration of penicillin. A second patient with a postoperative cholangitis and possibly a liver abscess recovered, but penicillin therapy did not appear to be responsible for the favorable outcome.

Toxic Manifestations

One of the outstanding features in this group of 200 patients was the extremely low incidence of toxic manifestations. While receiving penicillin two individuals had an unexplained rise in temperature which promptly subsided to normal when administration of the drug was discontinued. A third patient developed urticaria after receiving penicillin for one week. Treatment was omitted for 24 hours, and when therapy with the same lot was instituted again urticaria did not appear. Three patients developed a thrombophlebitis at the sites where penicillin had been given intravenously.

Summary and Conclusions

Penicillin is the most effective agent available for the treatment of staphylococcic infections. This also applies to some types of infection due to hemolytic streptococci. There is evidence that some green-producing strains of streptococci and non-hemolytic streptococci are highly resistant to penicillin. It may be anticipated that penicillin will reduce the mortality rate from pneumococcic and staphylococcic meningitis. The drug is also effective in the treatment of meningococcic meningitis, an infection which also responds readily, in most instances, to the sulfonamides. Encouraging therapeutic results have been obtained in infections of the lungs due to pyogenic, Gram positive cocci, and to the pneumococcus. Suppurative empyema and pericarditis may be controlled with penicillin in many cases without the necessity of surgical drainage of the cavities. The anticipation of a more hopeful outlook for patients with subacute bacterial endocarditis because of penicillin must be tempered by a cautious interpretation of clinical data, and treated patients must be checked periodically for evidence of the disease. Penicillin is the drug of choice in the treatment of gonorrhea with and without complications such as arthritis. More data are necessary before ascertaining the value of penicillin in the therapy of genitourinary tract infections other than gonorrhea. Penicillin should be evaluated further in the treatment of generalized peritonitis where preliminary observations appear promising. The drug may be of value in controlling some cases of actinomycosis.

Since penicillin is highly specific in its antibacterial action, it is exceedingly desirable that the physician should obtain all the precise bacteriological data possible before instituting therapy. This is particularly important during the present time when the material available for civilian use is limited. The physician should also remember that the sulfonamides still occupy a respected position in the treatment of infections, particularly in instances in which penicillin is of no benefit.

Although an extraordinary amount of information has accumulated in a relatively short period of time concerning penicillin, there remain some unsolved clinical problems that will require further clinical experience before their solution is at hand. One pertains to the optimal doses of penicillin to be used in a specific infection. Because the supply of the drug continues to be limited considerable stress has been placed on the minimal requirements. Although the majority of patients may respond favorably to the minimal doses set up, a continuance of such a philosophy is fraught with two potential dangers. First, an infection may be controlled but not eradicated. Second, there is the possibility that penicillin-resistant strains may develop and may be disseminated. In our own experience, two patients with staphylococcic sepsis were treated with what were believed to be adequate doses of penicillin but the infections were not completely brought under control. After the conclusion of therapy, staphylococci isolated from local lesions were found to be much more resistant in vitro than the parent strains obtained before therapy was instituted. There is a possibility that the use of inadequate doses of penicillin in patients with gonorrhea may cause the development of strains of gonococcus resistant to penicillin. Finally, further investigations should determine whether penicillin given concurrently with the sulfonamides may yield better results in the treatment of certain types of infections.

SEPTIC PULMONARY INFARCTION; REPORT OF 8 CASES*

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The clinical features of pulmonary infarction in general are well known and have been a popular topic in recent literature. On the other hand, the manifestations of septic pulmonary infarction in particular have received comparatively little attention except for occasional case reports. It is the purpose of this report to present the diagnostic aspects of this type of infarction and to emphasize that prompt surgical treatment may be of great importance in its prevention. The cases reported here have been selected partly with a view to calling attention to some of the less common sources for pulmonary infarcts.

In any case of septicemia caused by a pyogenic organism, abscesses may occur in the lungs as well as elsewhere. In a sense, these are embolic abscesses, but we have not included cases of this type in this discussion. Rather, we have been interested in the situation in which a septic thrombus in the peripheral veins or in the right side of the heart becomes dislodged, enters the pulmonary circulation, and causes infarction. The infarcted area in this event is infected from the start as opposed to the occasional case of a bland infarct which becomes secondarily infected by contamination through the bronchial tree.[1] Some idea of the comparative rarity of septic pulmonary infarction can be gained from the report of Hedblom[2] to the effect that in 528 collected cases of pulmonary abscess only 3.9 per cent were of certain or probable embolic origin.

Pulmonary Infarction Following Pharyngeal Infection

Case Reports

Case 1. L. J., a 39 year old negro, was admitted to the hospital complaining of severe sore throat of three weeks' duration. He was semicomatose and unwilling to open his mouth because of pain. The patient was acutely ill, groaning and stuporous. The temperature was 102° F., pulse 110, and respirations 22. The sclerae were moderately icteric. There was marked swelling of the left anterior faucial pillar and both tonsils were enlarged. Below the angle of the left mandible there was a fixed, tender, indurated mass. The submaxillary lymph nodes on the left were palpable. Fine moist râles were present over the lower part of the right hemithorax posteriorly. There was marked tenderness and moderate rigidity over the right upper quadrant of the abdomen.

The urine contained a trace of albumin and was positive for bilirubin. The red cell count was 3,600,000; the white cell count 14,100 with 73 per cent neutrophiles, 12

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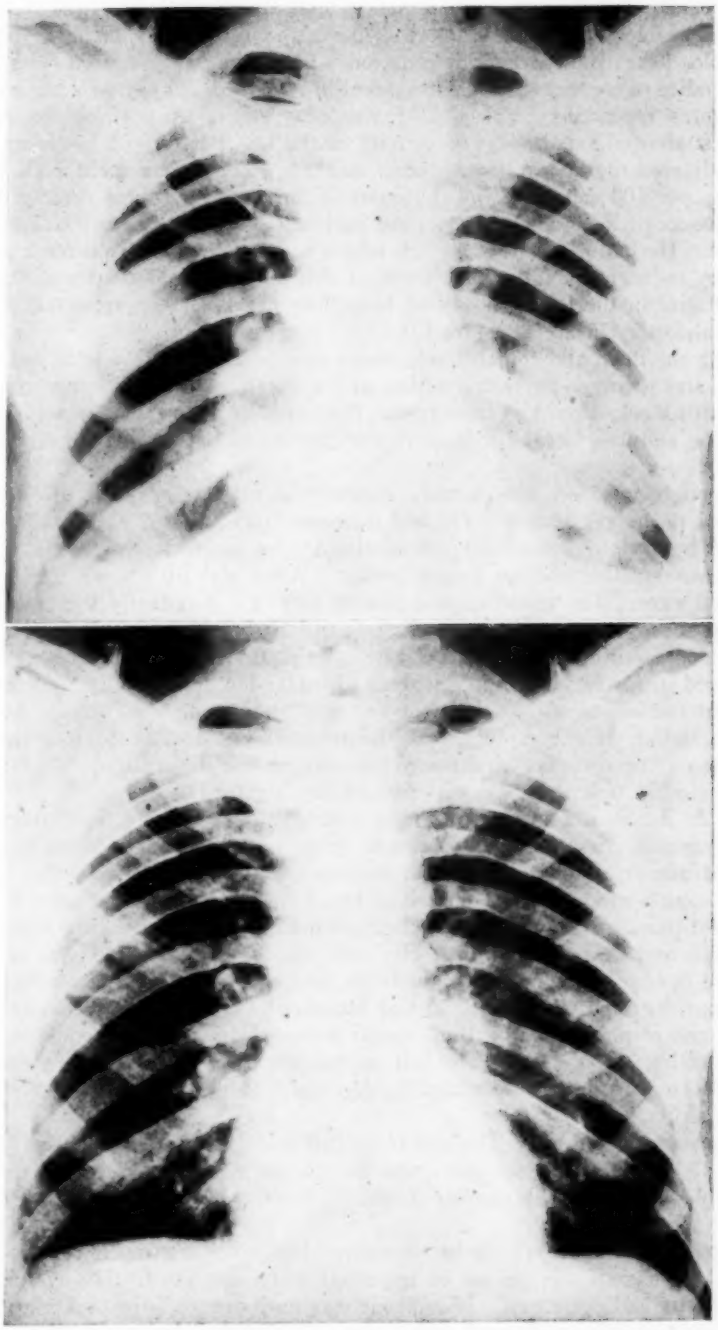

FIG. 1. (*above*) (Case 1) Rounded areas of increased density in lower halves of both lung fields suggesting pulmonary infarcts.
FIG. 2. (*below*) (Case 1) Clearing of infarcts with residual fibrosis.

per cent bands and 15 per cent lymphocytes. A blood smear was negative for sickling. The blood Kahn reaction was negative; blood urea nitrogen 60 mg. per 100 c.c.; blood creatinine 3 mg.; icterus index 96. The agglutination tests for spirochetal jaundice were negative. Throat culture yielded *Staphylococcus aureus,* and blood cultures repeatedly showed *Staphylococcus albus.* A portable roentgenogram of the chest showed small areas of opacity in the lower halves of both lungs.

Sulfadiazine therapy was instituted, and the blood levels were kept between 6 and 10 mg. per 100 c.c. The inflammation of the throat subsided rapidly during the first two weeks of hospitalization, but the patient continued to be critically ill, febrile, and icteric. He had developed a cough which was productive of purulent and bloody sputum. A roentgenogram of the chest at this time showed scattered areas of increased density in the lower halves of both lung fields. Their appearance suggested multiple pulmonary infarcts (figure 1).

During the third and fourth weeks there was general improvement, but the cough continued, and roentgen-ray examination of the chest showed no change until the end of the fourth week when rarefaction was discernible in some of the areas of infarction. Blood cultures were still positive for *Staphylococcus albus* and slight jaundice remained.

His cough subsided considerably during the fifth week, and the sputum was mucoid and no longer bloody. He had occasional episodes of chest pain which was intensified by coughing and deep breathing. The mass at the angle of the left mandible was smaller and no longer tender. After the fifth week the temperature was normal except for an occasional rise to 100° F. Gradually the cough and expectoration disappeared, and the swelling at the angle of the jaw became barely palpable. Blood cultures were negative after the sixth week. Roentgenograms of the chest showed steady regression in the areas of infarction, but a cavity 2 cm. in diameter appeared at the left base. The patient felt well at the time this was noted, however, and was gaining weight rapidly. At the time of his discharge from the hospital, after 82 days, the roentgenogram was negative except for residual fibrosis in some of the previously described areas of infarction (figure 2).

Case 2. L. S., a 24 year old negro, entered the hospital complaining of a sore throat, fever and chest pain. Four weeks prior to admission he developed a severe sore throat accompanied by fever and malaise. The following week he noticed the onset of a cough which was productive of blood-streaked sputum on several occasions. He also had pain in the front of his chest on the left side. This pain was intensified by coughing and deep inspiration. His sore throat continued but was less intense. During the next two weeks his cough, fever, and chest pain became worse.

The patient appeared acutely ill and jaundiced. His temperature was 101.5° F., pulse 110, and respirations 28. Both tonsils were enlarged and pus could be expressed from the follicles of the left. The left submaxillary lymph nodes were enlarged and tender. Motion of the left hemithorax was restricted, and there was a friction rub in the left axilla.

The urine was normal. The red blood cell count was 3,000,000; the white blood cell count 18,800. The icterus index was 56. Blood cultures were negative, and there were no blood agglutinins against *Leptospira icterohaemorrhagiae* and *Leptospira canicola.*

The patient received no specific therapy. His fever continued for the first eight days. At the end of this period he appeared much improved. His cough was less, and his icterus had decreased. His throat was no longer painful. A roentgenogram of the chest at this time showed round areas of opacity with rarefaction in the central part of one of these areas (figure 3). Convalescence was uneventful until the seventeenth hospital day, when a tender, movable mass was felt medial to the lower third of the left sternocleidomastoid muscle. At this time there was again mild fever

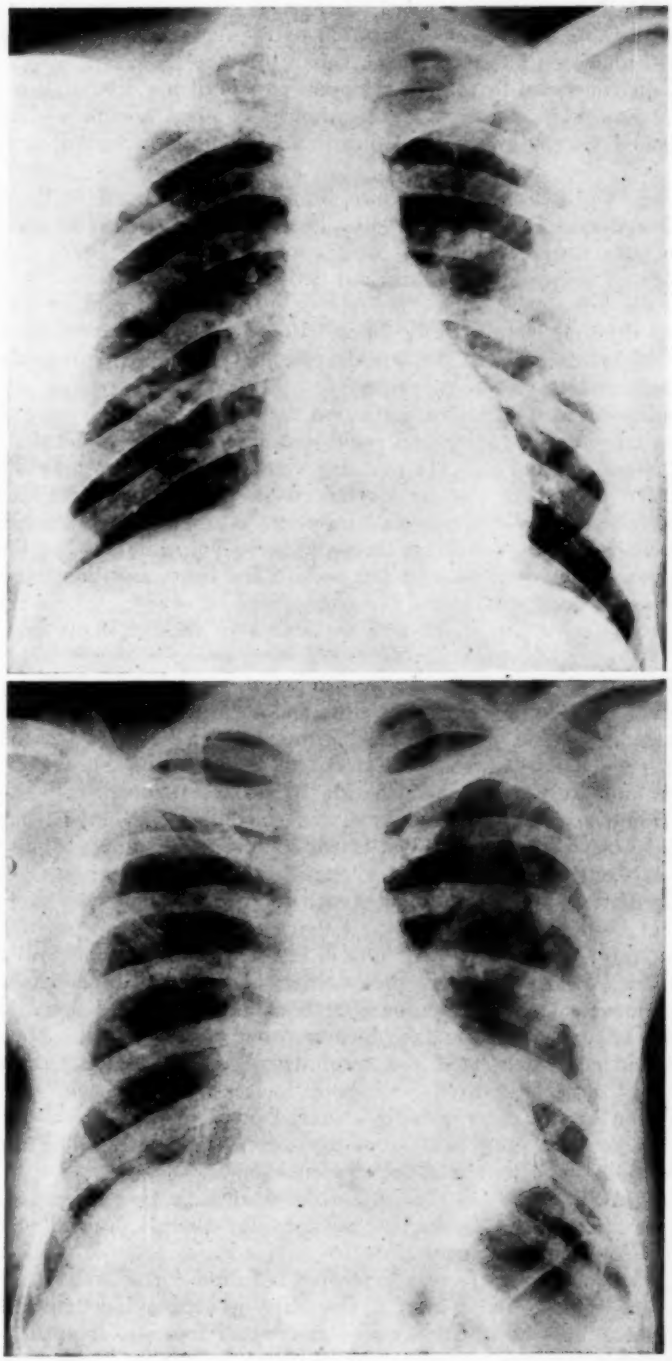

FIG. 3. (*above*) (Case 2) Rounded areas of opacity with central rarefaction in both lungs.

FIG. 4. (*below*) (Case 4) Areas of increased density in lower half of left lung.

for a few days. The mass was treated by roentgen-ray irradiation and was observed to shrink considerably. Surgical exploration of the mass disclosed a small collection of pus and a thrombosed internal jugular vein.

The patient continued to remain symptom-free until his discharge on the thirty-ninth hospital day. His roentgenograms showed gradual complete clearing of the pulmonary lesions except for residual fibrosis and pleural thickening in the involved areas.

Case 3. E. G., a 28 year old white woman, was admitted to the Georgetown University Hospital on December 4, 1940. Her illness had begun six days before admission with sore throat, chilliness, prostration, and fever. There had first been typical findings of follicular tonsillitis, and two days later a peritonsillar abscess had developed on the left side. During an episode of vomiting the abscess had ruptured and had been draining continuously since. Fever and severe prostration had persisted. The day of entrance to the hospital she had developed pain in the left flank, aggravated by breathing and by movement.

On examination at the time of admission the patient looked acutely and seriously ill. The respirations were noisy and rapid and accompanied by dilation of the alae nasae. The blood pressure was 118 mm. Hg systolic and 72 mm. diastolic, pulse 128, temperature 100° F. There was great enlargement in the left tonsil area where there was a ragged hole from which pus was draining. The right tonsil was inflamed but not much swollen. The cervical lymph nodes were not enlarged but there was exquisite tenderness of the left side of the neck. The heart and lungs were negative. When the patient's body was raised she complained of severe pain in the left flank. The abdomen was tense and there was tenderness in the left flank and at the umbilicus.

The urine contained a moderate amount of albumin but was otherwise normal. The erythrocyte count was 4.46 million; the leukocyte count 16,600 with 73 per cent segmented neutrophiles, 12 per cent band forms, and 15 per cent lymphocytes. The blood culture yielded no growth. *Streptococcus viridans* and *Staphylococcus aureus* were obtained on culture of the pus draining from the left tonsil.

Sulfapyridine was administered from the start, and the blood level was maintained above 10 mg. per 100 c.c. The urinary and blood findings altered little from day to day, except that mild anemia developed by the fourth hospital day and persisted in spite of transfusions of 500 c.c. each of whole blood given every other day. On the second hospital day it was noted that the patient was coughing frequently and unproductively. She still looked quite ill but she was having no pain and the neck was less tender. Moderate fever, tachycardia, and polypnea persisted, and slight cyanosis was noted. There was dullness at both lung bases and bronchial breathing over the right. From this day on she became progressively worse. The temperature and pulse fluctuated widely, and the respirations were variably shallow and continuously rapid. Râles appeared over both lower lobes in back, and a portable roentgen-ray film of the chest showed scattered opacities throughout the right lung and opacity of the left lung field from the second rib down. The roentgenologic diagnosis was bilateral generalized bronchopneumonia.

On the eighth hospital day the patient coughed up a plug of material from the left side of her throat, after which the peritonsillar abscess drained more profusely than ever. The next day she complained of severe pain in the left side of the neck, and by the following day there was extensive cellulitis. The area was treated with roentgen-ray irradiation, and within a few days it became fluctuant. It was then incised, using local anesthesia, and a large amount of foul pus escaped. Soon thereafter there were indications of peripheral circulatory collapse which became steadily worse. The patient died on the thirteenth hospital day.

Necropsy demonstrated that the abscess in the neck extended down to the inferior

margin of the thyroid cartilage in the pretracheal fascia. The left internal jugular vein was thrombosed. There was bilateral empyema. The lower lobe of the left lung was completely atelectatic. The left upper lobe and the right middle and lower lobes contained innumerable discrete abscesses, varying in size from 0.25 to 1 cm. in diameter. Almost all of the abscesses were located in the periphery of the lungs.

Discussion

These three cases represent examples of septicemia and pulmonary infarction accompanying pharyngeal infection. The pathogenesis of this type of septicemia has been summarized in articles by Hall[3] and Boharas.[4] These authors describe several modes of development of the process. It may follow almost any type of infection in or around the tonsil. In the cases that we have reported there was obvious acute tonsillitis, and in two of them a peritonsillar abscess was present. In some cases the initial focus of infection may remain unknown, and the condition may be recognized by signs of thrombophlebitis of the internal jugular vein. Hall[3] has reported that the picture of septicemia, with or without pulmonary involvement, may occur days or even weeks after the manifestations of local involvement in the pharynx have subsided. This latter type of case perhaps needs special emphasis because of the comparative obscurity of the focus of the disease.

An infection of the tonsil or peritonsillar area may reach the systemic circulation by producing thrombophlebitis of the tonsillar and peritonsillar veins. This thrombotic process may then extend into the internal jugular vein. Although this mode of involvement is stated to be rather less common, it appears to have been the one operating in Cases 1 and 2. More commonly thrombophlebitis of the internal jugular results from direct extension of the inflammatory process from the pharynx by way of the parapharyngeal space as exemplified in Case 3. The parapharyngeal or pharyngomaxillary space is posterior and lateral to the tonsil and separated from it only by the superior constrictor pharyngeus muscle. It must be understood that similar involvement of the internal jugular vein may result from infections in other locations than the tonsil, provided the area of infection is in contact with the vein or is drained by veins which empty into the internal jugular.

The local manifestations of pharyngeal infection complicated by septicemia are variable. Case 1 illustrates the fact that there may be no local signs except the ones ordinarily encountered in cases of uncomplicated pharyngeal inflammation. Here the clue to the diagnosis was to be found entirely in the systemic manifestations. It is only when the parapharyngeal space is the site of a phlegmonous inflammation that local signs may be prominent. With involvement of the parapharyngeal space there may be swelling and induration over the parotid gland and below the angle of the jaw and peritonsillar swelling and induration with few or no signs of pharyngitis. With extension of thrombophlebitis into the internal jugular vein there may be tenderness and swelling along the anterior border of the

sternocleidomastoid muscle. Of all the local signs tenderness at the angle of the jaw is most frequently noted. In one of our cases (Case 2) there was frank evidence of periphlebitis of the internal jugular vein, indicated by the considerable swelling, tenderness, and induration along the sternocleidomastoid muscle. It is interesting that the phenomena appeared in Case 2 some days after all other local and systemic manifestations of disease had subsided. In Case 3 there was persisting evidence of a peritonsillar abscess and tenderness at the angle of the jaw until about 48 hours before death, at which time the rapidly developing cellulitis of the neck probably resulted from extension of an infection from the parapharyngeal space.

The general symptoms encountered in these cases are those that might be expected in any similar septicemia. Jaundice was present in two of our cases and, as is true in most cases of septicemia, was of the hepatocellular type. In spite of the obvious clinical evidence of blood stream infection in all cases, blood cultures were negative in all but Case 1 in which the *Staphylococcus albus* was obtained. The general experience with the disease under discussion indicates that blood cultures are positive in only about half the cases.

The pulmonary lesions in the three cases reported above were a prominent feature. Although the systemic effects of the local disease were obvious in all cases, the appearance of the pulmonary lesions was the first clear indication of the need to search for a focus of thrombophlebitis. This fact was not accurately appraised during life in Case 3, mainly because the roentgen-ray appearance of the pulmonary disease was interpreted as bronchopneumonia. In Cases 1 and 2, the chest films were typical of pulmonary infarction, showing well defined, scattered areas of increased density. Recognition of the septic nature of the infarcts was facilitated, as serial films demonstrated the development of a radiolucent center and at times a fluid level in some of the previously homogeneous shadows (figures 1 and 3). This kind of cavitation is not peculiar to septic infarcts, however, for lung abscesses may develop in cases of bland infarcts as a result of infection extending from the bronchial tree.[1] In Case 3 bilateral empyema was discovered at autopsy. This complication is not unusual in cases of embolic lung abscesses, since the peripheral location of the lesions favors involvement of the pleura by the infecting organism. In addition to pulmonary abscesses, there may occasionally be other metastatic suppurative lesions in almost any location. Other serious but less common complications have been reported [3, 4] but hardly require enumeration here.

The serious nature of this type of sepsis can be emphasized by the fact that the mortality is high in untreated cases. Formerly, it was agreed that the only effective form of treatment was surgical, consisting of the provision of adequate drainage for any accumulated pus, with or without ligation of the internal jugular vein. Without this form of treatment the mortality was almost 100 per cent. It may be that the use of sulfonamides and penicillin will materially reduce the mortality rate in cases in which surgical treatment

is delayed or not employed. Our Cases 1 and 2 confirm this impression. However, it is not to be understood that we condone a program of treatment which does not include surgical measures, particularly ligation of the internal jugular vein. In summary, the treatment should consist of controlling the septic focus by chemotherapy and surgical drainage if necessary. Isolation of the septic focus from the circulation is accomplished by means of ligation of the internal jugular vein. When the vein is thrombosed, ligation should be performed below the thrombus to prevent embolism or further propagation in this direction and above the thrombus to prevent retrograde extension toward the brain. The treatment of metastatic abscesses requires chemotherapy and surgical drainage where practicable. The pulmonary lesions are usually not susceptible of surgical treatment because they are multiple. In the rare case of a solitary metastatic lung abscess operation may be necessary.

Pulmonary Infarction Complicating Bacterial Endocarditis

Case Reports *

Case 4. C. S., a 38 year old negro, had begun taking heroin three months before admission to the hospital. The drug had been suggested by a friend as a means for relieving cough, anorexia, night sweats, and vague chest pain. The heroin had been administered daily and intravenously without use of sterile technic. The cough continued, and he observed increasing fatigue and the loss of 18 pounds during the three month period. Because of these symptoms and the onset of fever and dyspnea he entered the hospital. A roentgenogram of the chest taken one week before admission had been reported as negative.

On examination the patient was acutely ill and dyspneic. The temperature was 102.5° F., pulse 125, and respirations 32. The only other positive findings included diminished breath sounds and subcrepitant râles over the left lower lobe posteriorly. The veins in the antecubital fossae and forearms were indurated as the result of intravenous administration of heroin. The urine was normal. The white blood cell count was 13,000 with 90 per cent neutrophiles and 10 per cent lymphocytes. The red blood cell count was 3,800,000. Roentgen-ray examination of the chest showed areas of increased density in the lower half of the left lung (figure 4). The heart showed a slight increase in its transverse diameter.

A blood culture taken on the third day was reported to show *Staphylococcus albus.* The patient was given sulfamerazine, and adequate levels were obtained. Repeated blood cultures showed *Staphylococcus aureus,* which was coagulase positive. A roentgen-ray film taken on the seventh hospital day revealed discrete areas of soft infiltration containing radiolucent centers scattered throughout both lungs (figure 5).

The patient continued to be extremely ill. He remained dyspneic and his temperature varied between 100° and 105° F. He coughed up blood-tinged sputum on several occasions. The white blood cell count ranged between 18,000 and 21,000. Frequent examinations of the heart failed to reveal any murmurs. A roentgen-ray film on the thirteenth day showed further cavitation in the many areas of infiltration scattered throughout both lungs. He died on the fourteenth hospital day.

Necropsy showed large friable vegetations on the tricuspid valve. Innumerable abscesses were present in both lungs, varying in size from 3 mm. to 2 cm. in diameter. Cultures obtained from the vegetations and from the lung abscesses were positive for *Staphylococcus aureus.*

* The following three cases were included in a previous report.[5]

Case 5. O. B., a 25 year old negress, gave a rather vague history, owing to the severity of her illness. Her health had been good until three weeks before admission when she had developed fever, vomiting, and symptoms of an upper respiratory infection. For one week before admission she had had a sore throat and cough.

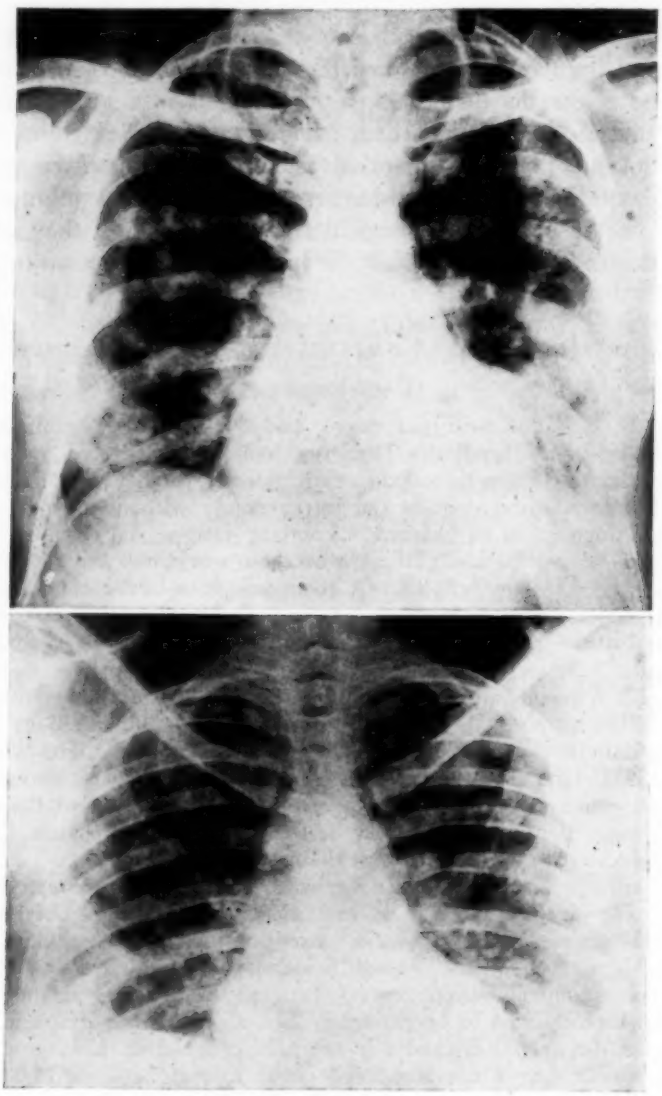

FIG. 5. (*above*) (Case 4) Multiple infarcts showing cavitation due to abscess formation.
FIG. 6. (*below*) (Case 5) Scattered small pulmonary infarcts.

Six days prior to entry she had rubbed her face and body with alcohol, then camphorated oil to alleviate a headache. The next day she broke out in welts and the following day began to peel. She stated that she was about six months pregnant.

The patient was well developed, slightly obese, stuporous, and acutely ill. Her

temperature was 102.5° F., pulse 130, respiratory rate 48 to 60. Her face was swollen and there was extensive patchy exfoliation over her arms and chest, leaving cracked and bleeding areas. There were several flattened bullous lesions on the arms. There were decreased resonance at the right lung base, increased breath sounds over both lung bases and infraclavicular areas, and fine moist râles in both axillae and over the right base posteriorly. The heart size was normal and there was a short soft systolic murmur to the left of the sternum. There was gallop rhythm. The uterus reached the umbilicus and fetal heart sounds were heard. Extensive raw areas were seen around the vulva.

A roentgen-ray film of the chest showed circumscribed areas of opacity scattered throughout both lung fields, suggesting pulmonary infarcts (figure 6). The urine contained a moderate amount of albumin. There was moderately severe anemia, which persisted throughout the course of the illness in spite of frequent blood transfusions. The leukocyte count was high, ranging from 12,300 to 20,500. Blood cultures were repeatedly positive for *Staphylococcus aureus*.

Sulfamerazine was first administered for 48 hours. The identity of the organism causing septicemia then being learned, penicillin was substituted. The day after penicillin was started the patient seemed slightly better. Her breathing was less labored, and she was slightly more alert. Fever and tachycardia persisted, however. On the next day pulsus alternans was detected, although the patient continued to appear somewhat improved. The skin lesions showed considerable healing. This improvement was transient, for on the sixth day she became extremely stuporous. Her respirations became more labored and the pulse considerably weaker. This downward course continued, and she died on the ninth hospital day.

It was subsequently learned from the patient's husband that she was addicted to the use of heroin. This drug was administered intravenously without aseptic precautions.

Necropsy revealed acute bacterial endocarditis of the tricuspid valve with multiple septic pulmonary infarcts which had progressed to form pulmonary abscesses. The six months fetus appeared to have been dead for several days.

Case 6. F. N., a 28 year old negress, had been having daily chills and fever for 10 days before admission to the hospital. Six days before admission she noted a sudden, piercing pain in the upper half of the left hemithorax, intensified by deep inspiration. A nonproductive cough began that day. She was seen by a physician who informed her that she had pleurisy and prescribed sulfathiazole. On the following day her cough became productive of a thick brown sputum. The cough and pain had continued.

The patient admitted having taken heroin intravenously for the preceding four months. The syringe and needle used for this procedure had not been sterilized. Her last injection had been given three weeks previously. She had lost 50 pounds during the period of her narcotic habit.

The patient was emaciated, dyspneic and complaining of chest pain. The temperature was 102.8° F., pulse 110, respirations 32, and blood pressure 100 mm. Hg systolic and 75 mm. diastolic. Both forearms were scarred along the course of the veins. There were bronchovesicular breathing and moist râles over the left upper lobe posteriorly. There was a soft systolic murmur heard over the mitral area.

The white blood cell count was 6,400 with 75 per cent neutrophiles and 25 per cent lymphocytes. Urinalysis showed a trace of albumin. Smears for malaria were negative. Roentgen-ray examination of the chest showed small areas of infiltration in the left upper lobe (figure 7). Repeated blood cultures were positive for *Staphylococcus aureus*. The patient was given sulfamerazine and supportive therapy. Because of the likelihood of acute bacterial endocarditis and pulmonary infarction, penicillin was not administered.

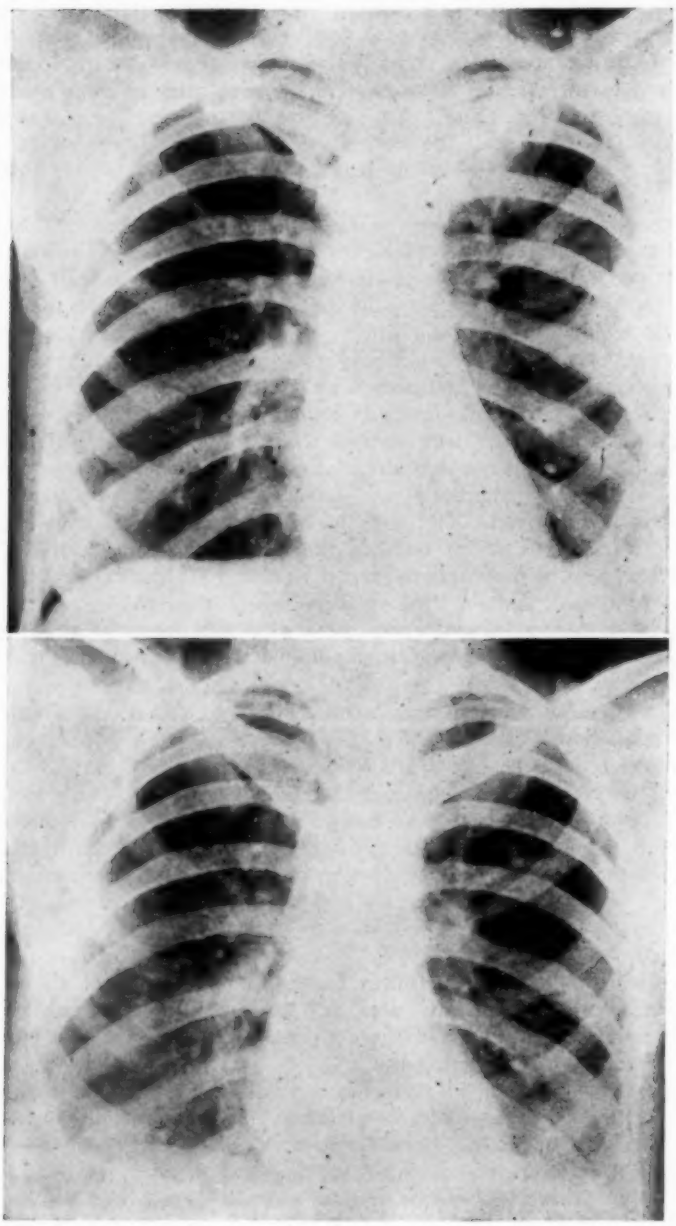

FIG. 7. (*above*) (Case 6) Infiltration in left upper lobe resembling minimal tuberculosis.
FIG. 8. (*below*) (Case 6) Wedge-shaped infarct in lower part of right upper lobe; clearing of left upper lobe.

There was no great change in the patient's condition during the following week except that the pain in her chest was less severe. On the seventh hospital day she expectorated blood-streaked sputum. This expectoration continued for the next few days at which time a roentgen-ray film of the chest showed clearing of the areas of infiltration in the left upper lobe and a wedge-shaped shadow of increased density in the lower lateral portion of the right upper lobe (figure 8). The remainder of the patient's course was rapidly downward. She was confused and her temperature varied between 100° and 105° F., with frequently recurring chills. She had repeated small hemoptyses. Physical and roentgen-ray examination disclosed many new areas of infarction in both lungs. No new heart murmurs were heard. The blood cultures continued to be positive for *Staphylococcus aureus*, and the red cell count showed a steady decline, although no evidence of jaundice appeared. She died on the thirty-first hospital day.

At necropsy there was acute bacterial endocarditis of the tricuspid valve. There were many pulmonary infarcts all of which had undergone abscess formation. There was empyema of the right pleural cavity. The spleen was moderately enlarged.

Discussion

These three cases of acute bacterial endocarditis are almost identical in every respect. All three patients were young negro adults who were addicted to the use of heroin intravenously. They developed *Staphylococcus aureus* septicemia, presumably owing either to contamination of the heroin or to lack of aseptic technic during injection of the drug. Acute bacterial endocarditis involving the tricuspid valve ensued in each case. In none of the cases was there evidence of preëxisting heart disease. From the focus in the right side of the heart septic emboli were carried to the lungs, resulting in infected infarcts and abscesses (figure 5). In Cases 4 and 6 the initial roentgenogram resembled minimal pulmonary tuberculosis (figures 4 and 7). However, in both cases the severity of the clinical picture was incompatible with this diagnosis. The correct clinical diagnosis was made during life in each case, when it was apparent that there was no other probable focus for the septic pulmonary infarcts than the right side of the heart. The absence of a diastolic murmur was presumptive evidence that the endocarditis involved the tricuspid and not the pulmonic valve. Treatment in all cases consisted of the administration of one of the sulfonamides and supportive therapy. In Case 5 penicillin was also used. None of the patients recovered.

Pulmonary Infarction Following Pelvic Thrombophlebitis

Case Reports

Case 7. N. W., a 37 year old negro multipara, had been pregnant about three months when she developed a severe chill, followed by fever. Two days later there were cramps in the lower part of the abdomen and vaginal bleeding began. A few days afterward, on June 6, 1943, she was admitted to the hospital.

On examination the patient did not appear acutely ill. Her temperature was 99° F., pulse 130, respirations 20, and blood pressure 120 mm. Hg systolic and 80 mm. diastolic. Her breasts were soft and contained colostrum. The heart and lungs were

normal. The uterus was twice normal size and a scanty, foul, reddish brown vaginal discharge was present. The urine showed one plus albumin and occasional red and white blood cells. The red blood cell count was 3,210,000 and the white blood cell count was 13,000. The Kahn reaction was negative.

Sulfathiazole was started on admission. During the next two days the vaginal bleeding increased and the temperature reached 103° F. The patient now complained of pain over the lower abdomen and there was tenderness in this area. The white blood cell count rose to 26,500. During the ensuing two weeks the temperature curve was of a septic character and varied between 99° and 105° F. On the twelfth hospital day there was sudden pain over the front of the chest on the right side, but roentgen-ray examination of the chest was negative. Blood cultures also were negative.

By July 5, one month after admission, the course was still septic. There was tenderness in the left adnexal region with some fixation and fullness and a profuse foul, yellow, vaginal discharge was present. On July 15 a roentgen-ray film of the chest showed diffuse mottling at the right base and a week later another film showed infarcts scattered throughout both lungs. At this time sulfamerazine was substituted for sulfathiazole. Blood transfusions were given frequently. There was now a cough which was productive of frothy, and occasionally blood-streaked sputum, but the patient appeared less ill than before. However, fever and leukocytosis persisted.

By August 5 the pelvic mass had decreased in size. The patient felt much improved and her temperature had been normal for 48 hours. She continued to be afebrile and to have a slight cough for the next week. At the end of this period a roentgen-ray film of the chest showed many cavities within the areas of infarction (figure 9). From this time until her discharge there was constant improvement. The roentgenograms of the chest showed many fluid-containing cavities which later disappeared to be replaced by strands of fibrous tissue (figure 10). The pelvic mass disappeared except for some adnexal thickening.

Case 8. L. B., a 24 year old negress, was admitted to the hospital complaining of intermittent, lower abdominal pain and vaginal bleeding of four days' duration. These symptoms had begun at a time when her menstrual period was about 10 days overdue. The day before admission she had observed a foul-smelling piece of tissue accompanying her vaginal flow.

On examination the patient did not appear ill. The temperature was 99° F., pulse 95, respirations 22, and blood pressure 110 mm. Hg systolic and 70 mm. diastolic. Protruding from the vagina was a large piece of necrotic placenta. The uterus was about three times normal size. The urinalysis was normal; white blood cell count 14,500; red blood cell count 4,300,000.

On the second hospital day she had a chill and her temperature rose to 101.5° F. There was no change in her physical examination. A blood culture taken at this time was negative. Sulfathiazole was started and adequate levels obtained. From then on her course was septic. The erythrocyte count declined and the leukocyte count was persistently high.

On the eighth hospital day tenderness was noted above the inguinal ligament on the right side. On rectal examination there was a hard, exquisitely tender mass which extended into the cul-de-sac from the right adnexal region. The impression at this time was pelvic cellulitis and pelvic thrombophlebitis. On the twelfth hospital day she developed a troublesome cough which was productive of slightly blood-tinged sputum. Moist râles were heard over the lower halves of both lungs. The impression was pulmonary infarction originating from a right pelvic thrombophlebitis. Roentgen-ray examination of the chest at this time showed diffuse mottling and many cavities in the upper halves of both lungs. A film made seven days later showed progression in the amount of infiltration and cavitation, and many of the cavities

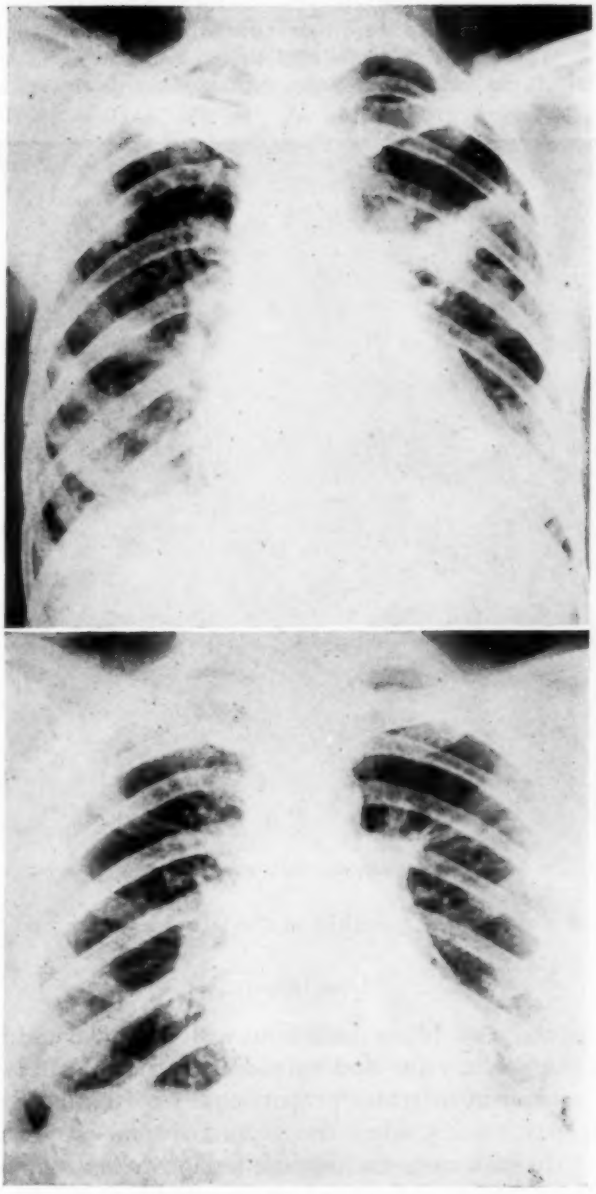

FIG. 9. (*above*) (Case 7) Multiple infarcts with cavitation.
FIG. 10. (*below*) (Case 7) Clearing of infarcts with residual strands of fibrosis.

contained fluid levels (figure 11). The remainder of the course was steadily downward, and she died on the twenty-fourth hospital day.

At necropsy there was an indurated inflammatory mass at the right of the cervix. In the center of this mass there were many dilated pelvic veins containing necrotic thrombi and pus. Thrombi were found in both common iliac veins and in the lower part of the inferior vena cava. The lungs contained many abscesses located at the

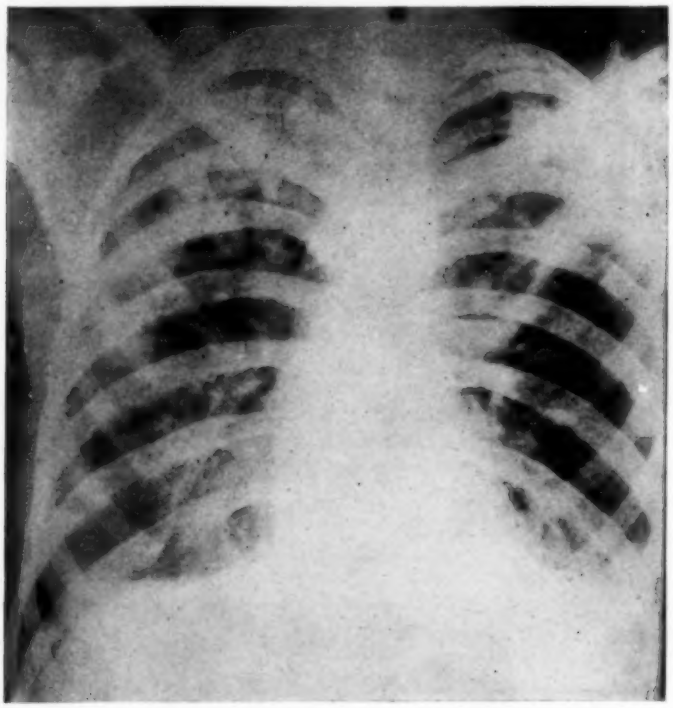

FIG. 11. (Case 8) Multiple infarcts with cavities, some showing fluid levels.

periphery. There was purulent pleuritis on the left side where one of the abscesses had ruptured.

DISCUSSION

These were cases of pelvic infection with secondary thrombophlebitis originating in the pelvic veins and extending variably. It is probable that the danger of embolism increases proportionally to the degree of extension of the process, particularly when the venous thrombosis reaches the common iliac vein. In both cases the pelvic infection followed abortion. There was a very hectic clinical course, which in each instance had its inception some days before the development of pulmonary infarction. In spite of the fact that there were clinical manifestations of septicemia, blood cultures were uniformly negative.

The roentgen-ray appearance of the pulmonary lesions varied. In the first chest film of Case 7 there was diffuse mottling which resembled the

picture of bronchopneumonia. In subsequent films there was the characteristic appearance of infarcts, later showing cavitation with and without fluid levels (figure 9). In Case 8 the first chest film was made at a time when the pulmonary infarcts had already undergone cavitation.

The treatment was similar in both cases, consisting of the administration of adequate doses of one of the sulfonamides, frequent blood transfusions, and other supportive treatment. One of the patients died; the other recovered after a prolonged, stormy course. The high mortality associated with this kind of illness emphasizes the need for improvement in therapy. Certainly, venous ligation performed with a view to isolating the thrombosed pelvic veins has much to recommend it in selected cases. In cases of severe pelvic infection a decision to ligate the common iliac vein or even the inferior vena cava is difficult to make, because the diagnosis of pelvic vein thrombosis usually must await the occurrence of pulmonary infarction or the development of edema of one or both lower extremities, indicating extension of the thrombotic process.

Summary

The eight cases presented here are examples of septic pulmonary embolism. They illustrate several of the sources from which such emboli may originate. Other sources, of course, can be called readily to mind, particularly lateral sinus thrombosis and septic thrombophlebitis of the peripheral veins. In three of the cases the failure to find any source for pulmonary emboli in the venous system permitted the diagnosis of acute bacterial endocarditis of the right side of the heart. In every case the pulmonary lesions were the first clear indication that a septic focus existed. This experience is not restricted to cases of septic pulmonary infarction. Pulmonary infarction in general is often the first obvious announcement of the presence of a thrombotic process in the veins.

The roentgen-ray appearance of the pulmonary lesions is variable. Bronchopneumonia may be simulated, or there may be a more or less typical rounded or wedge-shaped peripheral opacity (figures 1 and 8). Some of the septic pulmonary infarcts rapidly develop central rarefaction, indicating abscess formation. The presence of a fluid level signifies that the abscess communicates with a bronchus. It is only in this event that there is likely to be purulent sputum. There is often an area of pneumonitis surrounding the septic infarct. The infarct may enlarge peripherally, because of increasing tissue destruction, and cause extensive pleuritis or even empyema. The lesion may resolve spontaneously and leave no trace or an area of pleural thickening or a strand of pulmonary fibrosis (figures 2 and 10). It is interesting that some of these pulmonary lesions that obviously have undergone abscess formation may resolve so completely without evident drainage. The type of pulmonary lesions described in these cases may occasionally be due to septicemia alone, but in this event there are often abscesses in the

other organs, whereas there were no metastatic abscesses in the cases reported here except in the lungs.

The systemic manifestations in all these cases are essentially those of septicemia. The blood cultures may or may not be positive.

There is no specific treatment for multiple septic pulmonary infarcts. The important consideration is isolation of the source of the emboli when this can be accomplished by venous ligation. The use of antibacterial agents and supportive therapy is indicated in all cases. To date there are no adequate measures for dealing with cases of septic pulmonary infarction resulting from acute bacterial endocarditis, with the possible exception of the somewhat encouraging results from the use of penicillin.

Conclusions

1. Eight cases of septic pulmonary infarction have been presented. The sources of the pulmonary lesions were a septic process in the pharynx, acute bacterial endocarditis of the tricuspid valve, and pelvic thrombophlebitis complicating pelvic infection.

2. The presence of septic pulmonary infarcts may be the first indication of the need to search for a septic thrombotic process in the venous system.

3. In appropriate cases it is important to ligate the veins through which the infected emboli enter the blood stream.

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MENINGOCOCCIC MENINGITIS: REPORT ON 165 CASES *

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During the period from July 1942 through May 1944, 165 cases of meningococcic meningitis were seen at the Highland-Alameda County Hospital. As this is a relatively large series, it was decided to report the group, especially since the mortality in the proved cases was 4 per cent.

Of these 165 cases, the spinal fluid showed meningococci on direct smear in 120 instances and positive cultures in an additional 30 instances, making a total of 150 cases in which the etiology was proved. The additional 15 cases were included because purulent spinal fluid was demonstrated, and they occurred during epidemic periods of meningococcic meningitis. Excluding these 15 unproved cases, the mortality rate for the series was 4 per cent. Including all cases, the mortality rate was 5.3 per cent.

The case and mortality distribution by age was as follows:

Age	Cases	Deaths	Mortality
0–1 year	14	1	7.1%
1–5 years	27	2	7.4%
6–20 years	41	2	4.8%
21–40 years	50	0	0.0%
41–60 years	30	2	6.7%
61–80 years	3	2	
Total	165	9	5.3%

In analyzing the causes of death, it was found that six of the nine deaths occurred in the first 24 hours of hospitalization, two of these clinically being Waterhouse-Friderichsen syndromes. One death resulted from undue delay in diagnosis, and only two deaths occurred after adequate treatment.

Petechiae were found in 32.7 per cent of the cases. This is considerably less than in most military series reported, and probably indicates that the cases were seen at a later stage of the disease.

Therapy

In adults, 5 grams of sodium sulfadiazine in one liter of physiological saline were administered intravenously and in most instances this was followed by 1 gram orally every four hours. It was only occasionally necessary to give subsequent doses of sulfadiazine parenterally, as the Levine tube proved to be an effective instrument for the administration of medication and fluids during coma. A fluid intake of at least 3 liters a day was

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maintained, and sodium bicarbonate was given to promote alkalinity of the urine.

In children, an initial sulfadiazine dosage of 0.1 gram per kilo. was administered parenterally followed by oral doses calculated on a basis of 0.2 gram per kilo.

In all instances an effort was made to maintain a sulfadiazine blood level of approximately 10 mg. per 100 c.c. The initial sulfadiazine blood levels which were determined at the end of 24 hours of treatment averaged 14.8 mg. per 100 c.c. for 130 patients; and 95 subsequent determinations averaged 9.8 mg. per 100 c.c. Sulfadiazine could usually be discontinued on the ninth day of treatment.

In the 165 cases, microscopic hematuria occurred in nine instances and gross hematuria only once. No other drug reactions were encountered.

We feel that meningococcus antitoxin has a definite place in the treatment of the patient who fails to respond to sulfadiazine in 24 hours, or who on entry gives evidence of an overwhelming infection. Meningococcus antitoxin was used in 39, or 23.6 per cent of the cases. In the age group below 10 years, antitoxin was used in 32.8 per cent. In this age group, the average total dose was 20,000 units, the largest dose being 80,000 units. In the age group above 10 years, the average total dose was 50,000 units, the largest being 120,000 units. The antitoxin was given in a single dose, one half intravenously and the remainder intramuscularly. No serious reactions were encountered although eight cases developed urticaria.

In certain instances repeated lumbar punctures were done to relieve increased intracranial pressure. The indications were Biot type of respiration, undue restlessness after mild sedation and bladder catheterization, and severe headache after mild analgesics had failed to give relief. We believe that lumbar puncture, with relief of increased intracranial pressure may in the occasional case be a valuable therapeutic adjunct and even a life saving measure.

The following sequelae were encountered: (1) relapse, with subsequent recovery in a three year old child who had been discharged two weeks previously; (2) ulceration of massive purpura in a patient who had no obtainable blood pressure on entry and a blood pressure which never exceeded 70 mm. Hg systolic and 40 mm. diastolic for the ensuing 24 hours and who eventually recovered; (3) complete quadriplegia and respiratory paralysis which was successfully treated with a respirator and repeated lumbar punctures; (4) ptosis of the right eye and unilateral optic atrophy; (5) two instances of purulent effusions into knee joints, both of which were sterile on culture and subsequently recovered without drainage; (6) two instances of questionable hydrocephalus in infants; (7) one purulent pleural effusion which was sterile on cultures and cleared without drainage; and (8) hemiplegia in a 59 year old hypertensive who also developed thrombophlebitis of the deep calf veins.

Summary

One hundred and sixty-five cases of meningococcic meningitis with nine deaths, or a mortality rate of 5.3 per cent, have been presented. Of 150 cases proved bacteriologically, the mortality rate was 4 per cent.

Sulfadiazine was the main therapeutic weapon, but meningococcus antitoxin and repeated lumbar punctures to relieve increased intracranial pressure were valuable adjuncts in certain instances. Sequelae and causes of death have been briefly discussed.

INFECTIOUS MONONUCLEOSIS; A STUDY OF 96 CASES *

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The study presented in this paper was undertaken for the purpose of evaluating the clinical and laboratory findings in infectious mononucleosis, and of attempting to clarify the criteria supporting the diagnosis of this condition. This statistical analysis is based upon a series of 96 consecutive sporadic cases of infectious mononucleosis observed at the Jewish Hospital of Brooklyn over a 10 year period. This is one of the largest series of sporadic cases of this disease to be reported. Free reference will be made to the literature for purposes of comparison and evaluation of our findings.

Definition. Infectious mononucleosis is usually defined as an acute benign infection of unknown etiology characterized by irregular fever, swelling of the lymph glands, sore throat, splenomegaly, and lymphocytosis with the presence of abnormal lymphocytes in the peripheral blood stream; the blood serum may contain antibodies against sheep erythrocytes in high titers.

Terminology. The term infectious mononucleosis is somewhat misleading in that it suggests that the disease is characterized by the presence of monocytes in the blood. However, it enjoys the widest usage of all names which have been employed in referring to this disease. Downey and McKinlay,[1] in 1923, suggested "acute lymphadenosis with lymphocytosis" as a fitting name for this clinical entity. The objection was raised that this title failed to indicate the benign nature of this condition as distinguished from the fatal outcome of acute lymphoblastic leukemia, another acute lymphadenosis. To obviate this objection, it has been suggested that the disease be called "acute benign lymphadenosis." Monocytic angina, lymphocytic angina, and lymphatic reaction also have been used in referring to this condition. Glandular fever is a frequently employed term, especially when referring to an epidemic form which occurs in children.

Historical. The first description of this disease to appear in the literature is credited to Emil Pfeiffer [2] who, in 1889, under the title of "Drüsenfieber," called attention to a symptom-complex occurring in children, which he considered to be infectious and of epidemic nature. He was impressed by the swelling of the lymph glands along the posterior border of the sternomastoid muscles, by failure of the glands to suppurate, the splenomegaly, hepatomegaly, and the favorable course. He also noted an associated catarrhal reddening of the fauces. He pointed out that the fever declined after

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several days, but glandular enlargement remained for a relatively long time.

Filatow,[3] four years before Pfeiffer's work appeared, described cases of acute enlargement of the cervical lymph nodes without associated inflammatory changes in the mouth, nose, or pharynx.

West,[4] in 1896, submitted the first report of glandular fever to appear in the American literature, in which he described a large epidemic in Ohio of three years' duration.

Isolated reports of glandular enlargement and lymphocytosis which were mistaken for acute leukemia were made by Türk,[5] Hall,[6] and others.[7]

In 1918 Deussing,[8] during an epidemic of diphtheria, separated several cases which differed from the others in that there was cervical lymphadenopathy as well as a generalized lymphadenitis with enlargement of the liver and spleen. There was a leukocytosis and marked lymphocytosis in the peripheral blood. These findings were noted in addition to the inflammatory lesions in the throat.

Sprunt and Evans,[9] in 1920, were the first to use the term "infectious mononucleosis" instead of "glandular fever" or "Pfeiffer's disease." They stressed the benign nature of this infection, reporting a series of six cases in young adults with fever, generalized lymphadenopathy, palpable spleen, and leukocytosis with lymphocytosis. They noted that the lymphocytes in the peripheral blood were bizarre in appearance, giving quite a varied blood picture.

Tidy and Morley,[10] in 1921, described an epidemic of glandular fever associated with lymphocytosis. They suggested that cases described earlier as acute leukemias with recovery were really examples of infectious mononucleosis. They also contended that infectious mononucleosis and glandular fever were one and the same disease.

An important contribution was made in 1932 when Paul and Bunnell[11] discovered that blood serum of patients with the sporadic form of this disease may contain antibodies against sheep erythrocytes in concentrations far above a normal titer.

Etiology

1. *Exciting factors.* The etiology of this disease has remained obscure since its earliest clinical recognition. It has come to be looked upon as a generalized infection, presenting multiple and varied manifestations which represent a protective reaction against some unknown offending agent. Whether the latter is viral, bacterial, or protozoan has never been conclusively established, although much has been written on this particular phase of the disease.[12, 13, 14] Staphylococci, streptococci, the spirilla and fusiform bacilli of Vincent, the *Bacterium monocytogenes hominis,* and a protozoon, Toxoplasma, have been suggested as the etiologic agents but none of these has been proved as such.

A great deal has been written concerning the relationship of infectious mononucleosis to leukemia, syphilis, rubeola and influenza. Here again,

however, there is no conclusive proof that the association of infectious mononucleosis with these diseases indicates anything more than a coincidence.[15]

2. *Predisposing factors:*

a. *Age.* Children and young adults are affected for the most part. Involvement of individuals above 40 years of age is infrequent. However, any age group may be affected. Cases of infants as young as seven months of age, as well as adults up to the age of 70, have been reported.[16, 17, 18] In the authors' series the age varied from 1 to 61 years. The distribution of the cases according to age groups is graphically represented in figure 1.

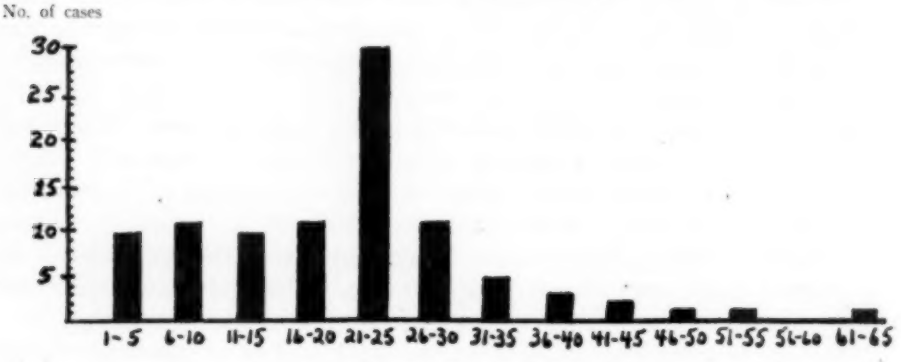

FIG. 1. Age groups.

Of the 96 cases studied, 83 (86.5 per cent) were between 1 and 30 years of age; 30 of these (31 per cent) were in the 21 to 25 year age group; 62 (64.5 per cent) were between 11 and 30. In Bernstein's[15] series of 65 cases, the age limits were 6 to 36 years, 78.5 per cent falling into the 15–30 year age group. Paul,[19] in his series of 51 cases, found the age limits to be 5 and 42 years, approximately 85 per cent falling into the 11 to 30 year group. Contrary to Paul's findings that only rarely was the disease observed on the pediatric service, a substantial number of the authors' cases (22 per cent) fell into the 1 to 10 year group.

b. *Sex.* Most authors have reported males to be somewhat more susceptible to the disease than females, usually in the ratio of 3:2.[20, 21] In our series this was confirmed, 54 males compared to 42 females being affected, roughly a ratio of 5:4.

c. *Race.* All of the cases herein reported occurred in white patients. This finding is in complete agreement with the previous literature. Only one instance of involvement of a negro has been reported.[22] It is felt that this is not explained by a racial predilection to the disease. Rather, it is probably due to the fact that hospitalization is not as accessible to colored people as it is to whites. In addition, their lower economic status often precludes an interruption in carrying out their occupational duties. There-

fore, it is probable that most cases of this disease occurring in the colored race are passed over as mild upper respiratory infections and the true nature of the illness is never established.

d. *Occupation.* The authors have found no predilection for any particular occupation. Our findings are listed in table 1.

TABLE I

Students	33
Salespeople	13
Office workers	12
Infants	8
Housewives	6
Physicians, nurses, medical student	5
Lawyers	4
Unemployed	4
Chauffers	3
Teacher	1
Writer	1
Shipfitter	1
Governess	1
Peddler	1
Mechanical Engineer	1
Tailor	1
Soldier	1

Early reports [9, 19] stressed the high frequency of occurrence of this disease in individuals who were associated with hospital work, i.e., physicians, nurses, medical students and laboratory workers. Our findings, as well as those of others,[15, 19] do not support this contention. It is felt that this impression arose because of the relatively easy accessibility of blood and serology studies to hospital workers.

e. *Season.* The seasonal distribution of the case studies of the authors is illustrated in table 2.

TABLE II

Season	No. of Cases	Per Cent of Total
Spring	33	34.3
Winter	25	26.0
Summer	22	23.0
Fall	16	16.7

These findings differ somewhat from those in the study reported by Bernstein [15] on 65 sporadic cases. Most of his cases (36 per cent) occurred in the fall season whereas only 14 per cent occurred in the spring. These statistics refer only to sporadic cases. Most epidemics of infectious mononucleosis have been reported as occurring in the spring [13, 23] and fall.[20, 24] Epidemics are rare in summer.[4]

Pathology. No autopsy material was available in our series because of the benign nature of the disease. Biopsy material, likewise, was unavailable since the diagnosis could be made by hematological and serological studies. However, Longcope,[22] Downey and Stasney,[25] Pratt,[26] and others,[23, 27, 28] have made detailed studies of the pathological changes encountered in this

disease. Grossly, the lymph nodes are described as being soft and spongy and the cut surface gray and granular. The outstanding features stressed by the above investigators on histological examination are hyperplasia of general and sinus reticulum, nodular foci of rounded reticulum cells, hyperplasia of follicles and germ centers in early cases and absence of follicles and germ centers in advanced cases. Dense areas of small lymphocytes and looser areas in which the lymphocytes vary in size and structure are seen. Large lymphocytes with pale nuclei and basophilic lymphocytes with lobulated nuclei in looser areas and sinuses are present. There is more or less obliteration of structure depending upon the degree of involvement. However, the architecture of the gland usually remains discernible. The same abnormal lymphocytes appearing in the peripheral blood stream may be seen in the glands.

Clinical Picture. Tidy [29] has classified this disease into three types depending upon the predominant clinical picture, as follows: (1) The glandular or Pfeiffer's type, occurring especially in children, in which the lymph node enlargement is the predominant feature. (2) The anginose type (monocytic angina). This clinical picture has often been confused with diphtheria. After a prodromal period of from one to three weeks, marked by increasing pyrexia and malaise, the throat becomes sore and a diphtheritic-like membrane forms on or near the tonsils and may persist for many days. (3) The febrile type. This is the most common type affecting adults. The onset is sudden with fever, headache and malaise. A macular or papular rash may then appear and not infrequently spots develop in crops. The glands may not become enlarged until two or three weeks after the onset of illness. The fever is of no characteristic type, is usually irregular, and persists for from one to three weeks.

Although most cases can be fitted into the above classification, the latter frequently proves inadequate because of the protean manifestations of this condition. Other workers [20, 30] have suggested a grouping dependent upon the individual sets of lymph nodes involved, emphasizing the thoracic, abdominal, and inguinal types of infectious mononucleosis.

The authors agree with the conception of infectious mononucleosis as a generalized infection in which the most characteristic feature at some time in the course of the disease is an increase in the mononuclear elements of the blood.[15] The further clinical features may then be considered and their relative importance evaluated.

As stated above, the clinical features of the disease are multiple. In addition, they may vary markedly in intensity. Indeed, individuals may be so mildly affected that the disease completely escapes clinical recognition. On the other hand, the patient may be so severely affected as to require many weeks of bed rest before recovery.

There are no accurate data as to the length of the incubation period. It has been reported variously as being from 1 to 28 days.[31, 32] However, the most nearly correct figure is considered to be about 11 days.[10, 16] Sus-

ceptibility to this disease is regarded as almost universal, but the degree of infectivity is not considered high. Epidemics have occurred especially in schools.

The type of onset varies widely. It may be sudden or gradual. The patient may present no complaints whatsoever and, indeed, the disease may go unrecognized through its entire course. More frequently, however, the onset resembles that of most acute infections with complaints of fever, headache, malaise, weakness, sore throat, chills, swollen lymph glands and gastrointestinal complaints. These may be mild or extremely severe with marked associated prostration.

Of the 96 cases of this series, the frequency of presenting symptoms is classified in table 3.

TABLE III

Fever	94	Diarrhea	4
Headache	34	Burning of eyes	3
Malaise	33	Joint pains	3
Sore throat	30	Epistaxis	2
Chills or chilly sensations	27	Sore gums	2
Weakness	22	Pruritus	2
Swollen neck glands	19	Drowsiness	2
Rash	16	Orbital pain	2
Abdominal pain	14	Chest pain	2
Nausea	13	Earache	2
Muscle aches and pains	11	Swollen inguinal glands	2
Cough	10	Dysphagia	1
Anorexia	9	Dizziness	1
Rhinitis	6	Bleeding gums	1
Vomiting	6	Convulsions	1
Constipation	5	Hematuria	1
Stiff neck	5	Painful axillary node	1
Jaundice	5	Puffy eyes	1

There were 36 subjective complaints presented in the 96 cases. The most frequent were fever (98 per cent), headache (35.4 per cent), malaise (34.3 per cent), sore throat (31.2 per cent), and chills or chilly sensations (28.1 per cent). These findings agree with those of most observers. The wide diversity of presenting complaints further testifies to the inadvisability of rigidly classifying this disease into types or groups.

A consideration of the essential physical findings in the present series of cases follows:

1. *Throat involvement:* 66 cases (68.7 per cent) presented evidence of throat involvement. Only 30 of these had subjective complaints of sore throat. The findings varied from a diffuse reddening of the pharynx to a typical follicular tonsillitis. No instances of ulcerative or membranous pharyngitis were encountered. Bernstein,[15] on the other hand, found ulcerative lesions of the pharynx in 19 per cent of his cases and membranous pharyngitis in 7 per cent. However, the frequency of throat involvement in this study compares favorably with that of McKinlay[33] (78 per cent) and with that of Bernstein[15] (77 per cent). No complicating Vincent's stomatitis was encountered in our entire series.

2. *Glandular involvement:* 76 cases (79 per cent) exhibited glandular enlargement. Of these, 22 patients offered complaints of swollen lymph nodes on admission. The frequency of involvement of groups of lymph nodes was as follows:

Cervical	72 cases
Axillary	28 cases
Inguinal	28 cases
Epitrochlear	9 cases
Mediastinal	3 cases

Thirty-seven of the 76 cases with lymph node enlargement had involvement of two or more groups of nodes. The remainder had involvement of isolated groups as follows:

Cervical	37 cases
Axillary	1 case
Inguinal	1 case

In most cases the lymph node enlargement appears in the first few days of the disease.[4, 30, 34] Less frequently adenopathy becomes evident in the second and third weeks of illness. A few isolated cases have been reported in which the glandular enlargement did not appear until after 25 days.[35]

All or any group of glands may be involved but the cervical group is preeminently affected. The glands are almost always discrete, occasionally in clumps, have a firm rubbery consistency and are usually only moderately tender. Enlargement is rarely symmetrical. The glands vary in size from 1 to 4 cm.

Axillary and inguinal nodes are less often involved than are the cervicals, but even the mediastinal and mesenteric groups may be involved, occasionally giving rise to pressure symptoms. The frequent complaints of abdominal pain in this disease are probably on the basis of mesenteric lymphadenitis.

3. *Splenomegaly:* The frequency of this finding has varied greatly in different reports. Davis [16] found the incidence to be 11 per cent in his series. Bernstein [15] reports an incidence of 64 per cent. Other workers [36] found splenomegaly almost in all cases ill enough to be confined to bed. Tidy [29] considers at least 50 per cent to be the probable incidence of splenic enlargement in this condition.

In the present study, the spleen was palpably enlarged in 69 cases (71.9 per cent). Of the remaining 27 cases, 20 demonstrated definite lymphadenopathy. The evaluation of the presence of splenic enlargement depends upon careful and repeated palpation. It is felt by the authors that 50 per cent is a very low figure for the true incidence of this finding in infectious mononucleosis.

Splenic enlargement, if present at all, was made out in practically all cases at the time of admission to the hospital which, in the majority of cases, was during the first week of illness. Only occasional cases developed palpable spleens under observation during the second week. The degree of enlargement was only moderate in almost all cases, reaching from 1 cm. to

4 cm. below the costal margin. Two cases in the present series demonstrated enlargement to 12 cm. below the costal arch. There have been rare instances in which the enlargement extended down to the level of the iliac crest.[37]

Splenomegaly may persist for weeks or even months. Baldridge et al.[26] reported the persistence of demonstrable splenic enlargement in a patient seven years following the acute illness.

Enlargement of the spleen without apparent lymphadenopathy was observed in 13 of the cases (13.5 per cent) studied by the authors. Absence of both splenomegaly and apparent lymph node enlargement was noted in seven cases (7.3 per cent). However, the possibility of lymphadenopathy in this group of 20 cases has not been excluded since the mesenteric, mediastinal, and other nodes not accessible to the tactile and visual senses may have been involved here. Tidy,[13] indeed, has stated that infectious mononucleosis without any glandular enlargement whatsoever is rare.

4. *Hepatomegaly:* Here again, as in the problem of splenomegaly, reports of the frequency of this finding vary widely. Gooding [23] found an incidence of 3.7 per cent in his series of 27 cases. Davis,[16] on the other hand, reported an incidence of 100 per cent. The authors found 26 cases (27 per cent) with hepatomegaly in the present study. Of these, all but two had associated splenic enlargement. Five of the 26 cases with hepatic enlargement had no apparent associated lymphadenopathy; four of these had palpable spleens. Therefore, one of the 26 cases with hepatomegaly had neither splenomegaly nor apparent lymphadenopathy.

5. *Rash:* Various types of cutaneous eruptions have been reported as occurring in this disease. Morbilliform, scarlatiniform, urticarial, vesicular, purpuric, petechial, typhoid-like, typhus-like, and other types have been described.

Paul [19] found cutaneous manifestations in 10 per cent of his cases. The authors found 18.7 per cent with skin lesions. These were present on admission to the hospital in practically all cases, appearing during the first few days of illness and usually lasting from one to six days. The majority of lesions observed were morbilliform in type, but urticarial, petechial, vesicular, and purpuric eruptions were also noted. Not infrequently combinations of these lesions were present.

6. *Jaundice:* Jaundice was observed in five cases (5.2 per cent). Bernstein [15] noted this finding in 1.6 per cent of his series. All five of our cases were of the obstructive type, four being associated with hepatic enlargement. The highest icterus index observed was 164. In all cases the icterus cleared gradually, signs of improvement appearing in the second week of the disease. Four of the cases involved demonstrated associated glandular enlargement.

De Vries [38] has suggested the following classification of jaundice occurring in infectious mononucleosis: *Type I,* in which jaundice is the first symptom and is followed after a variable period by glandular enlargement. *Type II,* in which the jaundice appears along with glandular enlargement. Four

of our five cases belonged to this group. *Type III,* in which jaundice occurs without apparent lymphadenopathy. One of our cases fell into this category.

The pathogenesis of the icterus occurring in the course of infectious mononucleosis has remained an unsettled problem. Whether it is due to glandular obstruction along the biliary tract or to an actual hepatitis is still the subject of much discussion. Morrison and Samwick [39] reported the presence of defective maturation of the red blood cell elements in the bone marrow of patients with infectious mononucleosis, suggesting a deficiency of erythrocyte maturation factor. This lack of the anti-anemic principle could be explained by defective absorption, storage, or utilization of same. The presence of jaundice, together with the above finding, draws attention to the liver as the site of altered physiology. Accordingly, therefore, Morrison [40] has suggested that the cause of jaundice in infectious mononucleosis may possibly be attributed to liver damage, either on a toxic or infectious basis. Further work, however, remains to be done before the pathogenesis of this finding becomes clear.

The significant laboratory findings in infectious mononucleosis are hematological and serological in nature.

1. *Hematological findings:* Leukopenia has been reported as a frequent observation in the early stages of this illness. Paul [19] observed this feature in approximately 50 per cent of his series of 51 cases during the first week of the disease, the lowest count recorded being 2,000 white cells per cu. mm. Bernstein [15] found the incidence of leukopenia in his study to be 10.8 per cent. A white blood count as low as 1,500 per cu. mm. has been reported in the literature.[41] In the present study leukopenia was observed in 38 cases (39.6 per cent), all occurring during the first week of illness. The lowest white count noted was 2,200 per cu. mm. In practically all of these patients the total white cell count returned to normal or above in the second week of the disease. This sequence of events has been reported previously.[19] It has been suggested that the oral lesions frequently seen in infectious mononucleosis may be related to the granulocytopenia so often observed at the onset of the disease.

Of the 58 cases (60.4 per cent) without leukopenia during the first week, practically all demonstrated leukocytosis. However, the highest white blood cell counts recorded were usually noted during the second week. The vast majority of patients had white counts varying between 10,000 and 20,000 per cu. mm. Only 10 patients (10.4 per cent) had counts above 20,000 per cu. mm. Of these, one had a count of 32,000 per cu. mm. and another had one as high as 43,000 per cu. mm. De Bruin [42] and others [29] report white counts as high as 63,000 per cu. mm. Only about 10 instances of counts over 40,000 per cu. mm. have been recorded in the literature. Of these, three have occurred in adults. The one case in our series with a count exceeding 40,000 per cu. mm. occurred in a 23 year old female.

Lymphocytosis has been found to be the most constant feature of the blood picture which is so characteristic of this disease process. In the

present study 80 cases (83.3 per cent) demonstrated lymphocytosis. This finding was observed to be most marked during the second week of illness, but it was also present in practically all of the cases to a lesser degree during the first week. Roughly, the increase in lymphocytes paralleled the degree of leukocytosis. However, lymphocytosis was present to a significant extent even in most cases where leukopenia was observed at the onset. In the differential white blood cell counts, the lymphocytes were found to constitute from 40 per cent to 90 per cent of the white cell elements, usually from 60 per cent to 80 per cent. Reports of 97 per cent lymphocytosis and higher have appeared in the literature.[7, 20] Toward the end of the third week the total leukocyte count, as well as the differential white cell count, usually begins to return to normal. However, the blood picture in a case reported by Farley[43] maintained its characteristics for as long as six and one-half years following the original illness.

There has been much discussion concerning the character and nature of the mononuclear cells appearing in the blood stream in this disease.[38,44, 45] It is felt by most authorities today that the specific cells which are responsible for the distinctive features of the peripheral blood smear in infectious mononucleosis belong to the lymphocyte series. Gall,[46] in his cytologic studies of this condition, came to the conclusion that these cells are atypical but relatively mature lymphocytes. They characteristically vary in size, morphology, and staining properties. The size varies from that of a small lymphocyte to that of a monocyte. The cytoplasm is typically deeply basophilic although it may be light; it may be vacuolated, giving the cell a foamy appearance. Azurophilic granules are frequently present. The nucleus may be round, oval, or indented and may occupy a portion or almost the entire cell. It may be centrally or excentrically placed and characteristically stains deeply, the chromatin appearing in clumps. Occasionally, fenestrations may be present, an appearance produced by actual holes piercing the nucleus in various directions.[47] In the present series of cases studied 74 (77 per cent) showed the type of cells described above.

The red blood cell count remained essentially unaltered throughout the course of the disease in all of our cases. This is in conformity with the findings of practically all other investigators in uncomplicated cases of infectious mononucleosis and is an important point in the differential diagnosis between this disease and acute leukemia.

The blood platelet count is usually within normal limits. However, thrombocytopenia has been reported with or without an associated hemorrhagic diathesis.[48, 49] In the present series, only one patient exhibited a paucity of platelets with an associated bleeding tendency, this being a known case of idiopathic thrombocytopenic purpura for years preceding the episode of infectious mononucleosis.

A positive blood picture was presented by 92 of our patients (95.8 per cent). No abnormalities were noted in the remaining four cases (4.2 per cent). One of these was observed from the early stages of the disease

through the entire course and presented splenomegaly with a strongly positive Paul-Bunnell test. The second case was seen after two weeks of illness with lymphadenopathy and a positive heterophile antibody test. The third was admitted after three weeks of the disease and presented lymphadenopathy, splenomegaly, and a positive heterophile antibody test. The fourth case was observed for the first time in the tenth week of illness and presented splenomegaly with a definitely positive Paul-Bunnell test.

2. *Serological findings:* Reference has already been made to the very important contribution of Paul and Bunnell [11] who demonstrated the presence of an unusual type of antibody in high concentration in the blood serum of patients with infectious mononucleosis. This antibody has been called appropriately a heterophile antibody for reasons to be discussed below, and can be readily demonstrated as agglutinins against sheep red cells. It can be differentiated easily from sheep red cell agglutinins which are normally present in the blood serum in low dilutions and from other antibodies [50] with similar characteristics by absorption tests.[41, 51, 52, 53] These absorption tests can be performed without difficulty by the ordinary clinical laboratories.

Although the real significance of the presence of this antibody in high titers in the blood serum of patients afflicted with this disease remains unexplained, the diagnostic value of this finding is widely recognized. This laboratory aid has considerably facilitated the diagnosis of infectious mononucleosis.

Much has been written concerning the nature of the antibodies involved in this disease.[11, 50, 54, 55, 56] Forssman,[57] in 1911, recognized the non-specificity of certain antigen-antibody reactions. The understanding of the principles underlying these reactions is mandatory for the comprehension of the serologic phenomena encountered in infectious mononucleosis. Heterophile antigens, when injected into certain animals, call forth the production of both specific and non-specific antibodies. The latter are demonstrable by their reactions with antigens other than those involved in their production. One such is the Forssman antigen which, when injected into rabbits or serologically similar animals, causes the production of hemolysins and agglutinins against sheep red cells.

Davidsohn [58] applied the Forssman principle clinically in his study of the heterophile response in the blood serum of patients who had received horse serum injections. The response observed was the production of lysins and agglutinins for sheep red cells. It was shortly thereafter that Paul and Bunnell, while studying heterophile antibody responses in various diseases, discovered a high titer of such antibodies in the blood serum of patients with infectious mononucleosis. Normally sheep red cell agglutinins exist in the blood serum of most individuals, but seldom in a titer above 1:8. Following the injection of horse serum, the agglutinin titer may reach as high as 1:64 or above. The antibody normally observed in the blood serum and that appearing after treatment with horse serum are of the Forssman type. The antibody observed in infectious mononucleosis exhibits clear cut dif-

ferences from the above, readily brought out by the absorption tests referred to previously. These latter are of great value in suspected cases of infectious mononucleosis where the heterophile antibody titer is low.

In a control study of sheep red cell agglutination titers on 46 hospital cases in which a diagnosis of infectious mononucleosis was not entertained, about 9 per cent had titers of 1:64. The remainder had titers below this level, in most cases 1:8 or 1:16. In our study, therefore, titers of 1:128 or above were considered positive Paul-Bunnell tests.

In the present series reported 64 cases (71.1 per cent) of the 90 in which the test was performed had sheep cell agglutinin titers of 1:128 or above. Two cases had titers as high as 1:8,000. The titer was not related to the severity of the disease or to the degree of lymphocytosis. Paul [19] reported positive tests in 90 per cent of his series and Bernstein [15] found an incidence of 92 per cent. Erf,[59] however, noted positive reactions in only 40 per cent of his cases. Other investigators [60] observed positive results in half of their cases. Davidsohn,[61] indeed, feels that the term seronegative might have to be employed in referring to many cases of infectious mononucleosis. Further work on the agglutinin absorption tests in cases with low titers may reduce the need for the use of this term. At the present time, however, it is fair to conclude that in the presence of a characteristic clinical and hematological picture, a negative Paul-Bunnell test does not preclude the diagnosis of infectious mononucleosis.

Regarding the time of appearance of a positive heterophile antibody test in this disease, experiences differ somewhat among various investigators. Paul [19] found low titers in the first week of the illness with the highest titers appearing during the second and third weeks. Bernstein [15] observed that the test was positive when first performed almost without exception, in cases where it became positive at all, most cases being seen in the first week of the illness. He feels that the test should be repeated for a month following the onset of illness in cases with negative results. Table 4 illustrates the time of appearance of positive Paul-Bunnell tests in the study of our cases.

TABLE IV

Stage of illness	No. of cases with positive Paul-Bunnell tests: Tested for 1st time	Became positive under observation	Total	
1st week	17		17	
2nd week	17	7	24	92.1%
3rd week	10	3	13	
4th week	4	1	5	
5th week	1		1	
6th week	1		1	
10th week	1	1	2	7.9%
12th week		1	1	
			Total = 64 cases.	

It can be seen from the table that 59 of the 64 cases (92.1 per cent) with positive Paul-Bunnell tests were positive during the first four weeks of the disease. Only one case was observed to develop a positive reaction during

the fourth week, preceding studies having yielded titers within normal limits. It is worthwhile noting, however, that one case developed a positive reaction during the tenth and another during the twelfth weeks of the illness.

Table 5 demonstrates the correlation between the blood picture and the heterophile antibody tests in our series of cases.

TABLE V

	% cases with positive blood picture	% cases with negative blood picture
Positive Paul-Bunnell test	66.9	4.2
Negative Paul-Bunnell test	28.9	—

Insufficient work has been done regarding the duration of the elevated sheep cell agglutinin titer found in the blood serum of patients with infectious mononucleosis. Davidsohn [41] reported an average duration of 56 days in 10 cases, with extremes of 26 to 114 days after the onset of illness. In one of our cases the elevated titer disappeared two weeks after the onset of the disease, and in two cases the return to a normal level occurred three weeks after the onset. Practically all other cases were clinically improved and discharged before return of the agglutinin titer to normal limits. Bernstein [15] found the usual duration of elevated agglutinins to be four to five months.

The occurrence of positive Paul-Bunnell reactions in conditions other than infectious mononucleosis is quite rare aside from the increased titer of sheep cell antibodies observed in individuals treated with horse serum, a strong fact in support of the diagnostic value of the test.

Since 1928 it has been observed repeatedly that temporarily positive serologic reactions for syphilis may occur during the course of infectious mononucleosis.[62, 63, 64, 65, 66, 67] In a series of 70 cases studied by the authors with Kline and Wassermann tests done repeatedly in most instances, no transient falsely positive serologic reactions were encountered. Paul [19] noted an incidence of 8 per cent. Another investigator [67] found temporarily positive reactions in 18 per cent. In a study in which samples of sera were tested for from one to three months after the acute disease, Asahina [68] found positive Wassermann reactions in about 40 per cent. When present, the duration of the positive reaction is brief, usually lasting only a few days. This factor may be responsible for the failure to demonstrate positive serology in many cases. Kahn,[69] however, reports a positive reaction lasting as long as three months.

The relationship between the sheep cell antibodies and the falsely positive serologic reactions for syphilis which occur in this disease has been studied rather intensively. It has been shown quite conclusively that the antibodies concerned in the Paul-Bunnell test on the one hand and in the Wassermann reaction on the other, are unrelated.

Falsely positive Widal reactions have been observed [54, 70] in this disease in addition to the previously described unusual serologic changes. Three

such instances were encountered in our present series. In two of these, typhoid H agglutinins developed in titers up to 1:160, and in the third a titer of 1:320 was observed. In each case the highest titer occurred at the time of greatest positivity of the Paul-Bunnell reaction and promptly fell within two to three weeks.

Clinical Course: The fever was irregular, varying between 100° and 106° F., usually between 100° and 103° F., with a tendency toward late afternoon and evening rises. The return of the temperature to normal was by lysis. The duration of the fever is illustrated in figure 2. The mean

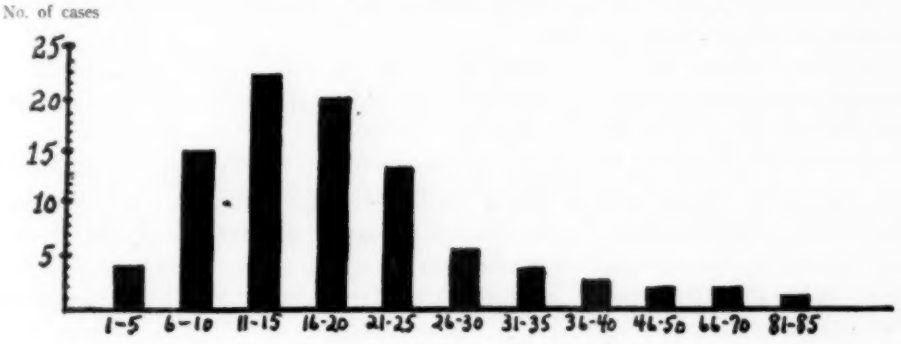

FIG. 2. Duration of fever in days.

duration of fever was 17 days, with extremes of three to 84 days. In 76.6 per cent of our series the febrile course lasted from six to 25 days. There was a sharp decline in the incidence of fever after the twenty-fifth day of illness. These findings agree with those of previous investigators.[17, 59, 71] Two of our cases were completely afebrile throughout the course of the disease. This is a very unusual feature, but Tidy and Morley [10] reported a similar finding in 1921.

Subjective complaints of headache, malaise, sore throat, chills or chilly sensations, weakness, abdominal pain, gastrointestinal disturbance and muscle aches and pains were frequent during the period of hospitalization, but disappeared after two to four weeks in practically all cases. Frequently, however, marked debility was observed to persist for a long period following an attack of infectious mononucleosis.

Relapses and septic complications may prolong the course of illness for many weeks.[16, 28] Recrudescences have also been noted not infrequently.[30, 60]

Differential Diagnosis: The protean manifestations of infectious mononucleosis frequently cause it to simulate a multitude of other clinical entities. Acute leukemia is one of the foremost conditions requiring differentiation. Absence of red blood cell changes, normal platelet count and absence of immature leukocytes militate against a diagnosis of leukemia. In addition, the Paul-Bunnell test is of great aid in doubtful cases. Granulocytopenia may also be confused with infectious mononucleosis, especially during the

early stages. The absence of mucous membrane ulcerations, as well as the benign course favors the diagnosis of infectious mononucleosis. The heterophile antibody test here also is of help. Diphtheria, Vincent's angina, Hodgkin's disease, tonsillitis, scarlet fever, typhoid fever, malaria, tuberculous adenitis, undulant fever and central nervous system infections may at times be mistaken for this disease, but hematological and serological studies should settle the issue.

Summary and Conclusions

1. A study of the findings in 96 consecutive sporadic cases of infectious mononucleosis has been presented.

2. The clinical and laboratory features in this series of cases were analyzed and compared with those of other investigators in an attempt to elucidate the diagnostic criteria for this condition.

3. The diagnosis of infectious mononucleosis is in order in the presence of a suspected clinical picture when the hematological findings are positive. The blood smear has been the most constant and characteristic single laboratory feature in the recognition of this disease.

4. A positive Paul-Bunnell test is strongly confirmatory, but its absence does not preclude the diagnosis. Only occasionally is this test positive and the blood picture unrevealing in a patient presenting the characteristic clinical features of this disease. It is sometimes necessary to repeat this test before a positive reaction develops.

5. Because of the extreme diversity of manifestations presented, the diagnosis may go unrecognized unless the disease is borne in mind and appropriate laboratory procedures carried out.

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PHLEGMONOUS GASTRITIS AS A MANIFESTATION OF SEPSIS *

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Historical Data

Phlegmonous gastritis has been known for many centuries. Galen [3] described symptoms that point to an "abscess or a phlegmonous or erysipelatous tumor of the stomach." Several physicians of the Middle Ages, for instance Avicenna,[1] Balescon de Tarente,[1] Piso,[1] and others, dealt with this subject. The first case report was written in 1594 by Forestus.[1] His diagnosis was made clinically. Since the patient recovered, we have no proof that the diagnosis was correct. In 1695 Sand [1] published the first case where the clinical diagnosis was confirmed at autopsy. Since then, reports have been more frequent. In 1919, Sundberg [1] was able to collect 213 cases of this disease by careful and extensive studies of the past and contemporary literature. In 1927, Gerster [2] accumulated another 47 publications including five reports of his own. Konjetzny [3] reviewed the subject formally in 1928. In 1938 Eliason and Wright [4] mention 276 cases, including two of their own and 29 collected reports. Since then, approximately a dozen additional presentations of case reports have appeared.

Case Reports

Case 1. S. T., a colored female, 23 years old, who worked as a nursemaid, was admitted November 23, 1941 and died December 5, 1941. There was no history of abuse of alcohol or previous illness. She was admitted for severe headache of two days' duration, pain in back of neck radiating to lumbar region and anteriorly to abdomen (not localized to any quadrant of the abdomen). She complained of anorexia, and weakness for the preceding few days, but no nausea or vomiting. Physical examination was negative except for soft apical systolic murmur and slight injection of the pharynx.

The temperature on the day of admission was 106° F., pulse 105 per minute, the blood pressure 110 mm. Hg systolic and 70 mm. diastolic. Urinalysis showed 1 plus albumin (patient was menstruating). Blood study revealed 3,400 white cells; the differential count showed 56 per cent polymorphonuclears, 3 per cent staff forms, and 41 per cent lymphocytes; the red cell count was 3,870,000 cells; the hemoglobin 84 per cent (Sahli). All serological tests were negative; all chemical determinations were within normal limits. The gastric juice was not examined. Throat cultures yielded *Staphylococcus aureus hemolyticus, Streptococcus hemolyticus.* The blood cultures on two separate occasions, i.e., three days after admission and just before death, were sterile. A flat plate on December 3, 1941 (two days before death) revealed marked gaseous distention (figure A) of the stomach.

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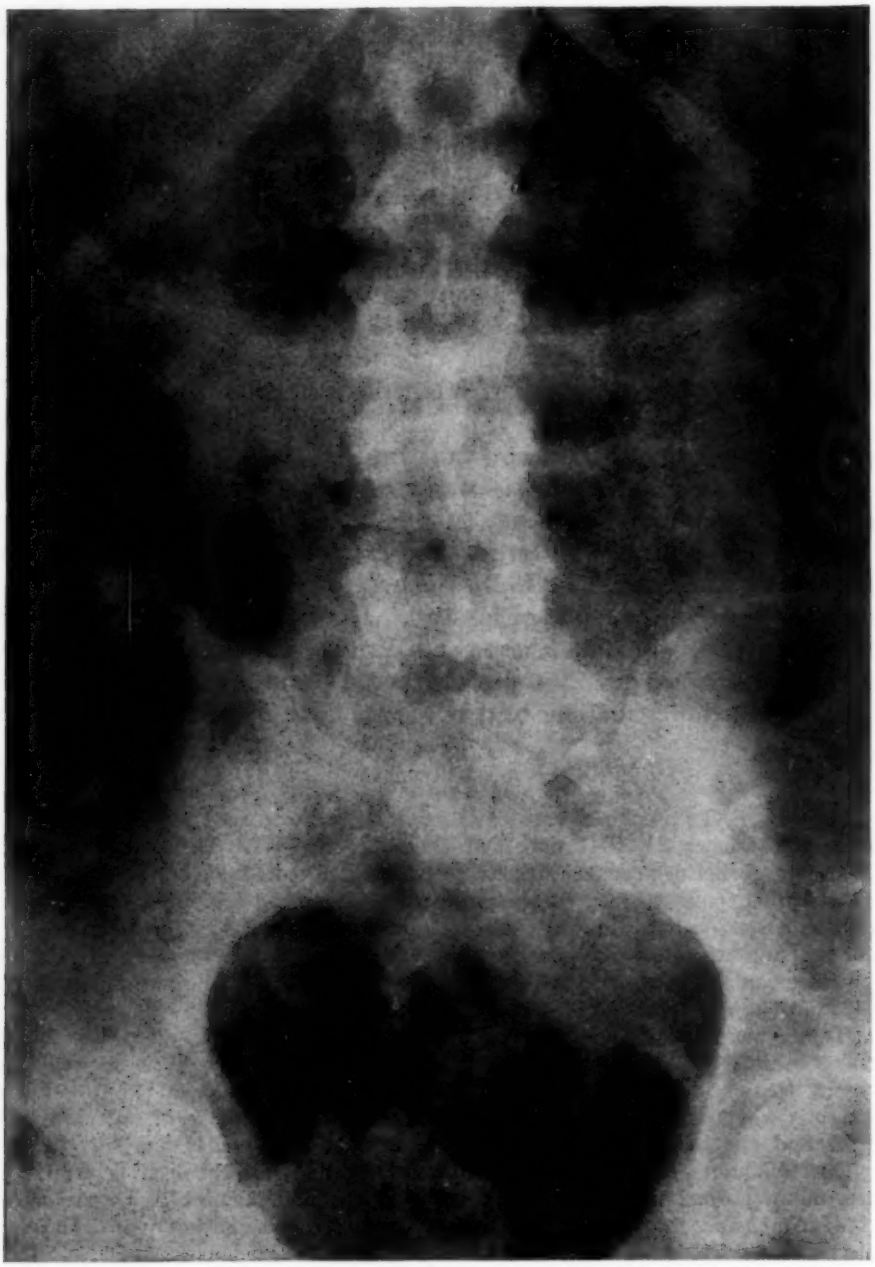


FIG. A. (*Case 1.*) Roentgenogram of the abdomen showing marked gaseous distention of the stomach.

Course. On the day after admission, whitish exudate with follicles on the left tonsil were noted. There was slight injection of the posterior aspect of the drum. The temperature ranged between 101° and 103° F. for the first 10 days, and then between 103° and 105° for the next five days. The patient's condition became progressively worse. She became incontinent, drowsy, and finally comatose. She died on the fourteenth hospital day, with a terminal temperature elevation of 108° F. She vomited twice on the day before death. The vomitus is described in the nurses' notes as a green fluid. (The patient received sulfapyridine during the last two days of her illness.)

At autopsy the pertinent description of the stomach was as follows. The stomach (figure 1) was dilated. On inspection some firmly adherent, yellowish sheets

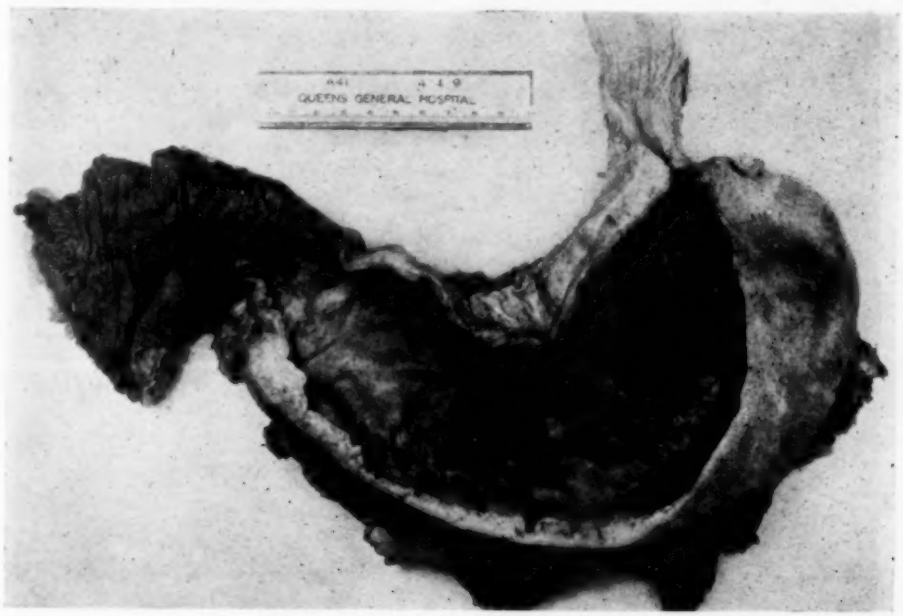


FIG. 1. (*Case 1.*) Gross appearance of the stomach showing the wall thickened by edema and exudate. Mucosal folds are prominent. Note the absence of involvement of the esophagus and of the duodenum.

of exudate were present over the lesser curvature near the cardiac end. The stomach wall was greatly thickened and edematous, especially in the region of the cardia. On section it measured almost 2 centimeters in thickness at these points. The rugal folds were noted to be well preserved, although much coarser and more rounded than ordinarily noted. The mucosa was dull and granular with areas of congestion scattered in various portions, especially near the cardiac end. On inspection of the sectioned wall, there was noted a uniform, thick, yellow layer, quite soft, which extended from just beneath the mucosa down to the external muscle coat. No distinguishing characteristics could be discerned in this area, and this process, although diffusely involving the entire stomach wall from the cardiac opening to the pylorus, diminished in intensity and extent of the involvement as the pylorus was approached.

The duodenum and esophagus showed no lesion grossly.

The microscopic appearance of the stomach was as follows. The *mucosa* was intact without ulceration. There was a moderate amount of inflammatory infiltra-

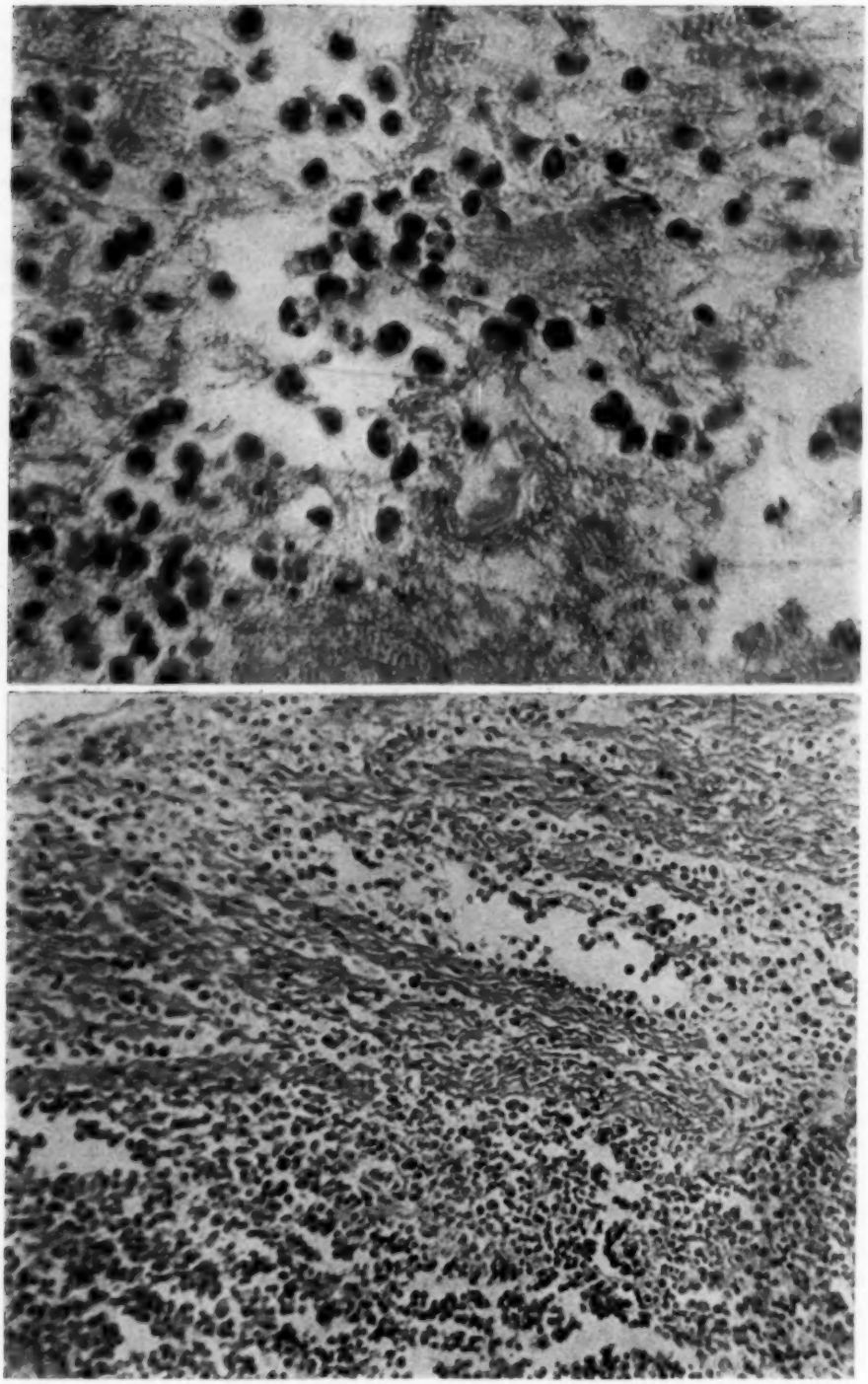


FIG. 1a (above). (*Case 1.*) H. P. microphotograph. Submucosa showing edema, fibrinous exudate, polymorphonuclear cell infiltration and labilized histiocytes.

FIG. 1b (below). (*Case 1.*) L. P. microphotograph. Muscular coat showing compact exudate, mainly polymorphonuclear in character. Note abscess areas.

tion and marked congestion. The *submucosa* (figure 1a) showed diffuse edema and fibrinous exudate. There was extensive inflammatory infiltration, lymphangitis, and venous thrombosis. In the *muscular coat* (figure 1b) the exudate was more compact. Abscess-like areas were apparently more marked than in the submucosa. The absence of edema may account for this appearance. There was marked lymphangitis. The *serosa* was edematous with a moderate number of inflammatory cells and some involvement of lymphatics.

The inflammatory cells of the mucosa were mainly lymphocytes. The exudate in the submucosa consisted mainly of polymorphonuclear cells and many labilized histiocytes. The same was true for the muscular and the serosal infiltration except that the polymorphonuclears appeared more numerous in the muscular coat.

The other pertinent anatomical findings were early peritonitis and left pleural and pericardial effusion, probably inflammatory in nature. In addition, acute hyperplastic splenitis was present.

The postmortem cultures of the peritoneum showed *B. coli,* and the left pleura showed *B. coli, B. pyocyaneus* and *Streptococcus non-hemolyticus.* No bacteria could be demonstrated in a histological section by Giemsa stain.

The final anatomical diagnoses were as follows: 1. Diffuse phlegmonous gastritis, with (2) extension to duodenum. 3. Early peritonitis. 4. Pleural effusion, left. 5. Pericardial effusion. 6. Acute hyperplastic splenitis. 7. Serous hepatitis.

Discussion of Case 1: The history and physical examination in this case offer little or nothing to suggest the diagnosis of diffuse phlegmonous gastritis. The pain in the abdomen at the time of admission (12 days before death), which is described as "radiating from neck to lumbar region and abdomen," has no obvious connection with the stomach ailment. We believe that the phlegmonous gastritis appeared later. Whether the vomiting one day before death was linked to the gastric lesion is open to doubt, since the patient had received sulfapyridine at this time.

The stomach at autopsy presented the usual picture of diffuse phlegmonous gastritis (figure 1). The extension of the phlegmon to the proximal part of the duodenum is noteworthy. This is an infrequent occurrence.

We are inclined to interpret this case as a hematogenous infection. The fact that the blood was sterile up to death, however, compels the consideration of the "direct type" of diffuse phlegmonous gastritis, that is, disease produced by swallowing of organisms from the tonsillar lesion. The peritonitis is considered as an extension of the phlegmon of the stomach. The pleural and pericardial effusion may also represent extension. The marked gastric dilatation seen by flat plate is noteworthy. Though this dilatation is not pathognomonic of this lesion and there are numerous conditions that can produce this picture, yet the procedure (flat-plate) would seem to be distinctly indicated.

Case 2. First admission January 12, 1942. Discharged April 21, 1942. Final admission May 15, 1942. Died May 29, 1942. E. M., an 11 year old colored girl, was admitted for painful cervical lymph node swelling, anorexia, fatigue, weight loss and migrating joint pains. There was a history of cough with blood-streaked sputum one year before admission.

Physical examination revealed a poorly nourished and poorly developed colored female with many enlarged, hard, discrete cervical, axillary, inguinal and epitrochlear

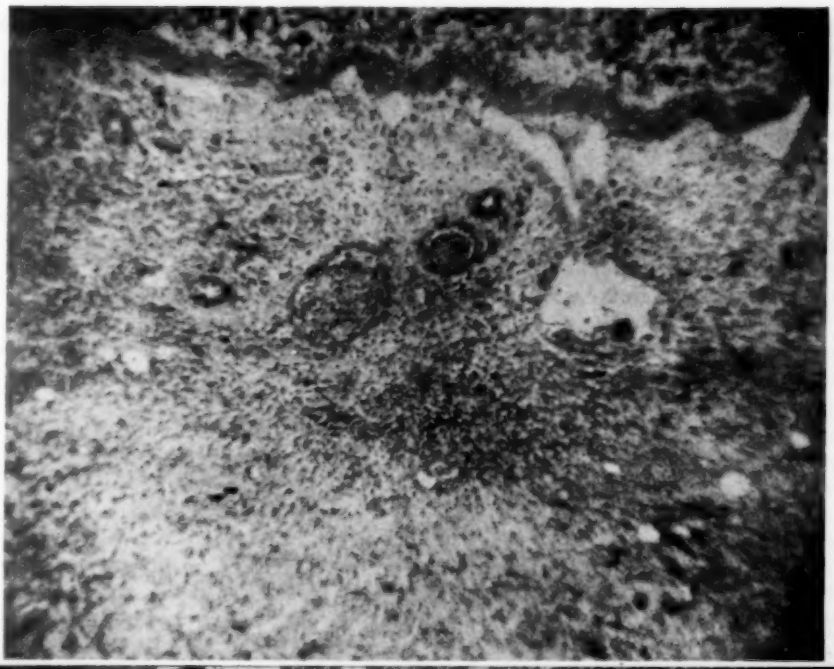
nodes. The parotid salivary glands also were swollen. The corrected sedimentation rate was 22 millimeters per hour. The patient was afebrile. Blood studies revealed 6,950 white cells, 32 per cent polymorphonuclears, 68 per cent lymphocytes, 3,800,000 red cells and a hemoglobin of 78 per cent (Sahli). Roentgenogram of the chest revealed large hilar nodes.

Course. After two weeks, the patient began to run a low grade fever. At six weeks she developed a butterfly rash over the face. A biopsy of the skin lesion and deltoid muscle suggested lupus erythematosus disseminatus. Eight weeks after admission, she developed a submental abscess which drained spontaneously. After that the temperature fell to normal and she improved generally. An electrocardiogram on April 6, 1942 showed changes similar to those of an anterior coronary occlusion. Two weeks later an electrocardiogram showed sinus tachycardia with left axis deviation and ST and T wave changes similar to those in active rheumatic carditis. The patient was discharged during the fourth month of hospitalization. She returned three weeks later because of weakness, left chest and precordial pain, dyspnea on exertion, and cough. Difficulty in urination and frequency were also present. Physical examination, in addition to earlier findings, revealed an injected pharynx, enlarged heart with sounds of poor quality and a short apical systolic murmur. The white cell count at this time revealed 6,000 cells, 80 per cent of them being polymorphonuclears, 20 per cent lymphocytes. The red cell count was 4,000,000, the hemoglobin 75 per cent (Sahli). The corrected sedimentation rate was 42 millimeters per hour. The urine showed 1 plus albumin. The temperature was 102° F. The roentgenogram of the chest on May 16, 1942 showed moderate thickening of lung roots with a few calcified hilar nodes, peritruncal thickening in the right lower lobe and right interlobar pleural thickening.

Course. Four days after readmission (May 19, 1942) she developed right pleural fluid. A chest tap yielded purulent material. A closed thoracotomy was done. On May 24, 1942, while chest fluid was being withdrawn a second time, the child had a clonic-tonic convulsive seizure for one to two minutes. The temperature remained high (from 101 to 104° F.). The white cell count rose to 26,000. The urine on May 26, 1942 showed granular and hyaline casts. On May 28, 1942, the day before death, the child developed coarse râles bilaterally, and the pulse became rapid and thready. She was confused at times. Twelve hours before death the patient complained of abdominal pain and vomited a large amount of dark green watery fluid. Four hours before death, she vomited again. The vomitus is described by the nurse as "a dark brown curdled substance with many threads of mucus." The nurse's note two hours before death reads again "patient vomited about three ounces of dark brown mucus." (Patient received sulfadiazine at that time.) The temperature rose to 104° F. terminally. The child died the fourteenth hospital day of the second admission and five months after the onset of symptoms. A blood culture (May 23, 1943) and cultures of pleural fluid (May 18, 1942 and May 24, 1942) revealed pneumococcus type 21. A blood culture (May 28, 1942) showed pneumococcus type 21 and *Streptococcus non-hemolyticus.* An electrocardiogram (May 28, 1942) showed sinus tachycardia.

At autopsy the pertinent description of the stomach was as follows. The wall of the stomach was markedly thickened throughout, measuring 7 to 8 millimeters in diameter. This thickening began abruptly at the cardia and ended abruptly at the pylorus. On section, the wall revealed infiltration by semiopaque grayish white material apparently in all coats of the stomach with the markings lost. There were numerous irregular, superficial ulcerations of the mucosa throughout, varying in size from 2 to 8 millimeters in diameter.

Microscopically the stomach showed the following picture. The *mucosa* appeared somewhat edematous. There was a moderate amount of cell infiltration, and digestive



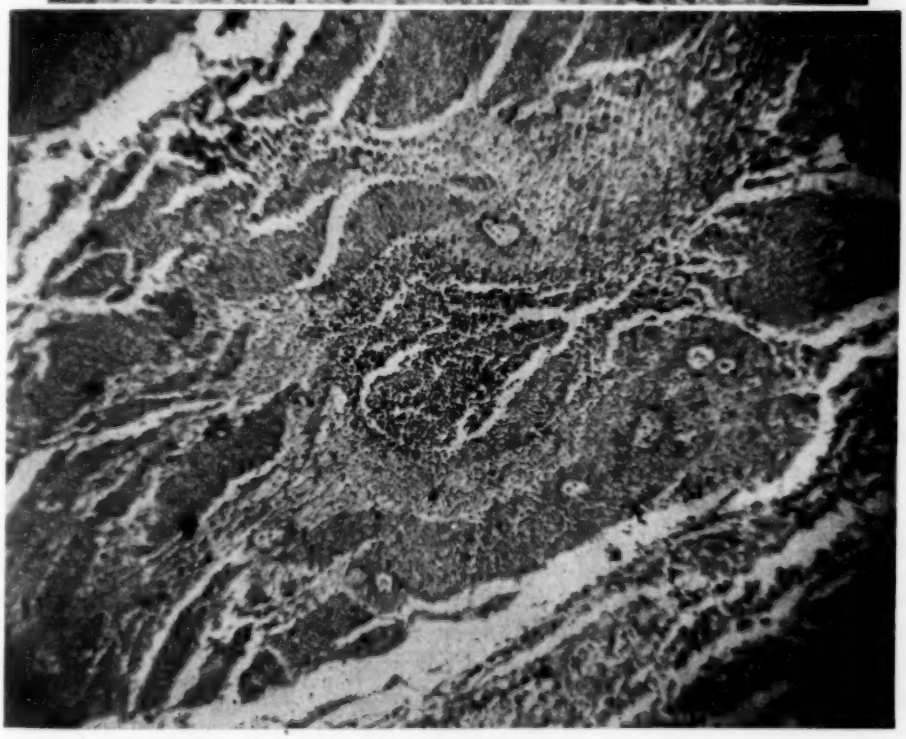


FIG. 2a (above). (*Case 2.*) L. P. microphotograph. Submucosa with extensive exudate. Small part of muscularis mucosae and mucosa shown above. Note vascular thrombi.
FIG. 2b (below). (*Case 2.*) L. P. microphotograph. Muscular coat showing cellular exudate with abscess formation.

erosions and ulcerations of the mucosa. The ulcers extended through the muscularis mucosa into the submucosa with marked basophilic staining of autolytic zones. This basophilia was particularly true for the basement membrane, reticulum, collagen material, and muscle. The *muscularis mucosae* showed some edema in areas which were not involved by ulceration. There was a limited amount of inflammatory cell infiltration. The *submucosa* (figure 2a) presented marked swelling and edema with extensive cell infiltration. Thromboses of venous channels and lymphatics were outstanding. The walls of some veins and lymph channels showed inflammatory infiltration. Intervening diffuse cellular exudate with some breakdown into abscess formation was present. The *muscular coat* was extensively involved by inflammatory exudate, particularly in areas of penetrating venules with thromboses of same. There were regional abscess areas with some destruction of muscle (figure 2b). The *serosa* showed edema with a considerable amount of inflammatory cells. Vascular channels were not included in the serosal sections. The inflammatory exudate consisted mainly of polymorphonuclears throughout.

The autopsy revealed the pathologic lesions of lupus erythematosus disseminatus as well as the findings produced by sepsis. The pertinent findings demonstrating sepsis were: superimposed bacterial growth on the atypical verrucous endocarditis, infected pleural effusion, organizing bronchopneumonia, hyperplastic splenitis, and finally phlegmonous gastritis and peritonitis.

The postmortem culture of the pleural fluid revealed pneumococcus type 21, *Staphylococcus aureus,* and *Streptococcus non-hemolyticus.* A postmortem culture of the peritoneum yielded pneumococcus type 21, *B. coli, Streptococcus hemolyticus* and *Streptococcus non-hemolyticus.* A culture from the mitral valve vegetation showed overgrowth by *B. coli.* Giemsa stains of a tissue section revealed large numbers of cocci with the morphology of diplococci in the submucosa, muscularis and serosa. Only very few cocci could be demonstrated in the muscularis mucosae and none in the mucosa.

The final anatomical diagnoses were as follows: 1. Lupus erythematosus. 2. Generalized lymphadenopathy. 3. "Wireloop" lesion of kidney. 4. Chronic active pericarditis. 5. Organizing bronchopneumonia. 6. Bilateral pleural effusion—infected. 7. Atypical verrucous endocarditis (Libman-Sachs) of mitral and tricuspid valves. 8. Superimposed bacterial endocarditis. 9. Septicemia—pneumococcus type 21). 10. Phlegmonous gastritis. 11. Peritonitis.

Discussion of Case 2: In this case the history and physical examination are slightly more suggestive of diffuse phlegmonous gastritis than in the first case. Twelve hours before death the child complained of abdominal pain (no exact description given) and vomited three times. In view of the pain we are inclined to attribute the vomiting to the stomach lesion, even though this patient had received sulfadiazine at this time.

The gross and microscopic findings in this case do not differ from the vast majority of reports of diffuse phlegmon of the stomach.

This case is interpreted as a case of lupus erythematosus disseminatus with bronchopneumonia and infected pleural effusion which led to blood stream invasion with manifestation of the latter in the superimposed bacterial infection of the existing endocarditis, as well as the phlegmonous gastritis. The peritonitis again should be considered as an extension of the stomach lesion. The positive blood culture is in favor of this concept.

Case 3. Admitted January 9, 1942. Died January 9, 1942. C. P., a 70 year old white male, was brought to the hospital in extremis. A fragmentary history

obtained from a son revealed that he had been ill with "chronic cough and heart trouble" for many years. Shortly before admission he became comatose and incontinent. There was no history of acute upper respiratory infection. Physical examination revealed an elderly white male in extremis. The ear, nose and throat examination revealed no lesion. The heart was not enlarged. No thrills or murmurs were heard. Apparent abdominal tenderness existed, for the patient grimaced when the abdomen was palpated. The patient died before a physical examination or laboratory studies could be completed.

At autopsy the pertinent description of the stomach was as follows. On opening the peritoneal cavity, a massive stomach was seen occupying almost the entire upper half of the abdominal cavity. The wall of the stomach (figure 3) was markedly indurated. The serosal surface near the fundus was covered by a small patch of

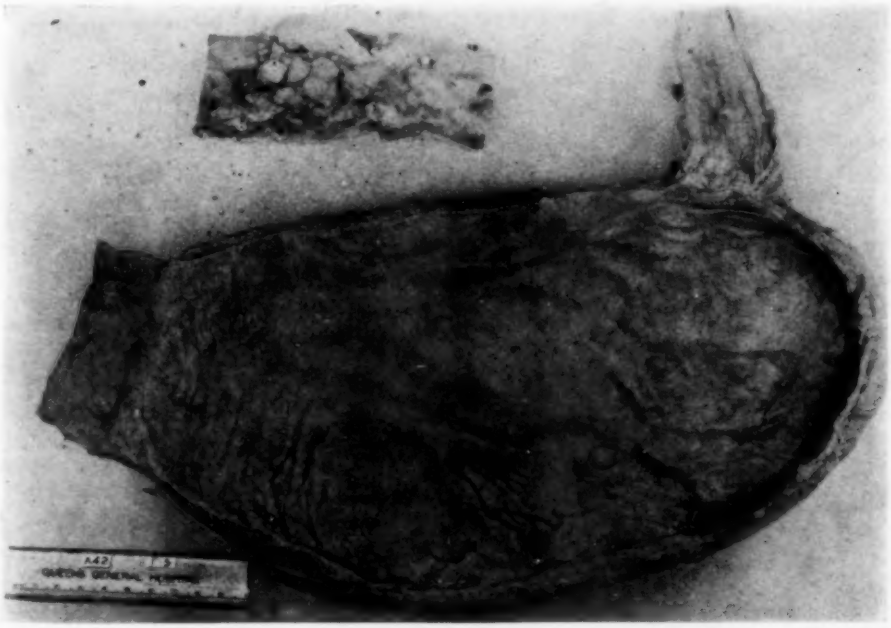


FIG. 3. (*Case 3.*) Gross appearance of the stomach showing marked dilatation and visible thickening of the stomach wall. Note the absence of involvement of the esophagus and the duodenum, and the numerous polypoid mucosal protrusions. Portion of aorta with enlarged adventitial lymph nodes is seen above.

friable, yellowish white exudate. The serosa was otherwise thin and glistening throughout. On section the entire stomach wall was seen to be markedly thickened, measuring at least 1½ cm. in thickness at its widest portion. The area of thickening extended throughout the entire stomach, from the cardiac orifice to the pylorus. The lesion was well demarcated from the regional esophagus and duodenum, which showed no gross evidence of the changes noted in the gastric wall. The muscularis was markedly thickened, with a definite translucency suggesting edema noted throughout. The submucosa was markedly thickened and edematous with many well demarcated, frankly necrotic areas scattered irregularly throughout. The mucosa appeared intact although it was moderately thickened. No evidence of ulceration was noted. There were seen approximately 10 large polypoid mucosal protrusions ranging in size from

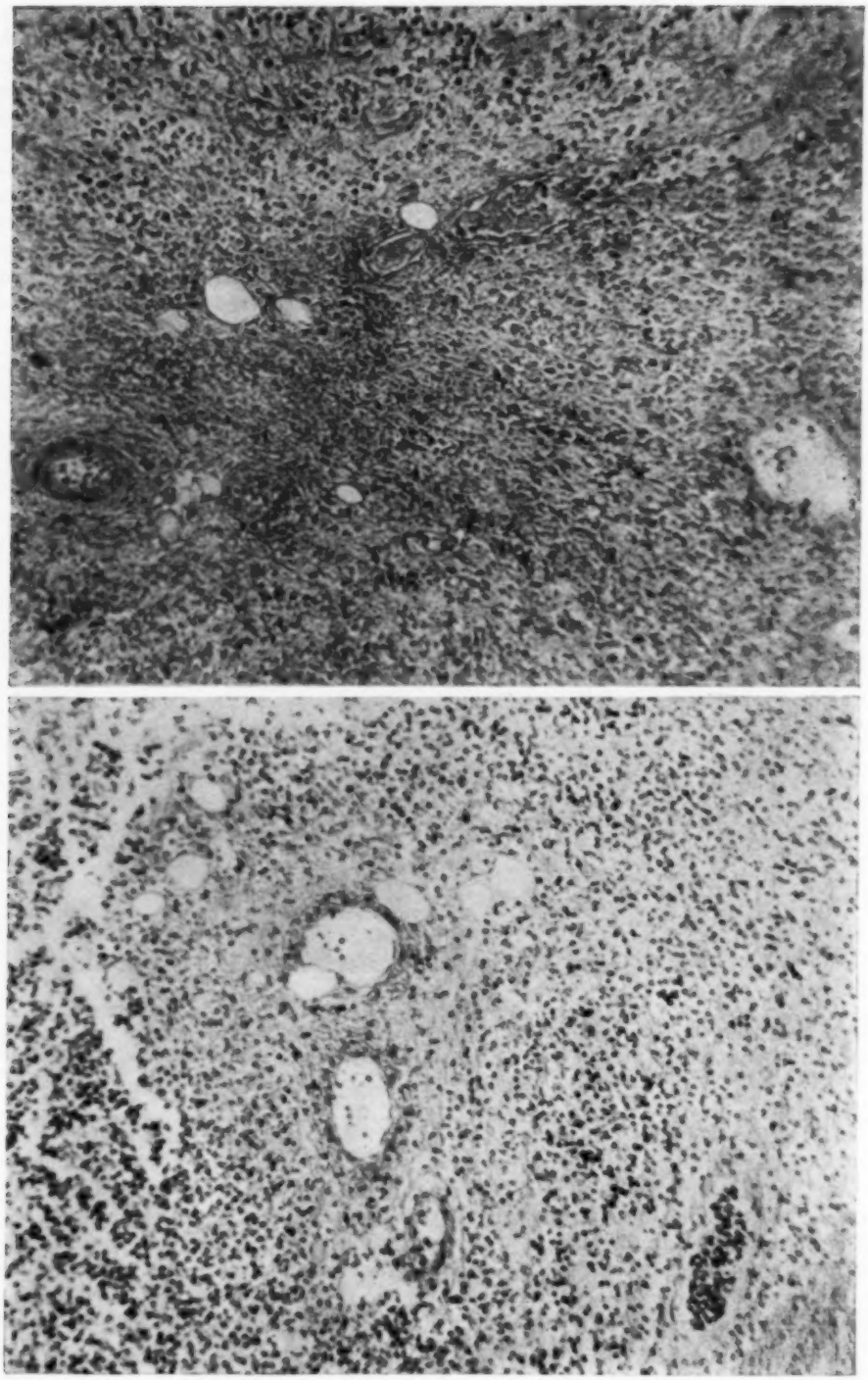


FIG. 3a (above). (*Case 3.*) L. P. microphotograph. Submucosa presenting arteritis, thrombi formation and diffuse exudation.

FIG. 3b (below). (*Case 3.*) L. P. microphotograph. Submucosa showing extensive polymorphonuclear exudate, fibrin about vessels, and a dilated lymphatic channel filled with cells, a prominent feature in this case.

½ to 2 cm. These polypoid structures were produced by protrusion of the underlying edematous swollen submucosa.

The microscopic appearance of the stomach was as follows: The *mucosa* showed extensive infiltration by inflammatory cells with separation of the glands which showed also dilatation and intestinal metaplasia. No ulceration was present. The *muscularis mucosae* presented cell infiltration which was more prominent in the deeper layer. In the *submucosa* (figures 3a and 3b) there was seen abundant fibrin, diffuse and extensive cellular infiltration with small abscesses and necrobiotic areas. The dilated lymph vessels were tensely filled with cells. Arteries and veins showed extensive inflammatory infiltration of the adventitia and media with prominent accumulation of fibrin surrounding veins, arteries and lymph channels, and fusing them together. Small hyaline thrombi were noted in capillaries, and cellular and fibrinous thrombi in small veins. The *muscularis* showed separation of bundles by edema and frank purulent exudate and fibrin with abscess formation. Some venous thrombi were present and distended lymphatics were filled with cells and fibrin. In the *serosal layer* the swelling was not marked, but there was considerable inflammatory infiltration and lymphatic distention.

The inflammatory cells of the mucosa were mainly lymphocytes, some large mononuclear cells, and very few polymorphonuclears. The muscularis mucosae showed similar exudate, more prominent in the deeper layers of the structure with the polymorphonuclears more numerous. The submucosa presented mainly polymorphonuclear exudate and the same was true for the muscularis which showed a few large mononuclear cells in addition.

Other noteworthy findings were early peritonitis, hyperplastic splenitis, hyperplastic lymphadenitis, and bilateral lower lobe bronchopneumonia.

Postmortem culture of the stomach revealed *B. coli, B. proteus* and *Streptococcus hemolyticus*. Culture of spleen and peritoneum yielded *Streptococcus hemolyticus*. Large numbers of cocci arranged in short chains were seen with the aid of Giemsa staining in the submucosa and in the muscularis. In the serosa the same organisms were found in diminishing numbers. No organisms could be located in the muscularis mucosae or mucosa.

The final anatomical diagnoses are as follows: 1. Diffuse phlegmonous gastritis, with polypoid protrusions. 2. Chronic gastritis. 3. Limited peritonitis. 4 Hyperplastic splenitis. 5. Hyperplastic lymphadenitis. 6. Sepsis (*Streptococcus hemolyticus*). 7. Bilateral lower lobe bronchopneumonia.

Discussion of Case 3: The history and physical examination were fragmentary and incomplete. The known data were irrelevant except for the grimacing on palpation of the abdomen. This finding in a comatose and moribund patient suggests severe tenderness.

The outstanding autopsy findings were the size of the stomach and the presence of about 10 polypoid protrusions into the lumen. The great enlargement of the stomach (it occupied almost the entire upper half of the abdomen) was due mainly to extreme dilatation. This feature of dilatation may be demonstrated by roentgen-ray as in case 1 (figure A), and this clinical form of the disease may be diagnosed by this means. The presence of multiple polypoid structures of the mucosa is a rather rare phenomenon. Except for the above mentioned facts this case differs little anatomically from the majority of published cases.

In view of the inadequate history and physical examination this case cannot be analyzed fully in regard to its etiology or pathogenesis. We are

tempted, nevertheless, to consider this a case of bronchopneumonia in a 70 year old man with sepsis following, and the stomach lesion occurring as a manifestation of the latter. The peritonitis, as in the first two cases, should be considered as an extension of the inflammatory process from the stomach. The presence of a chronic gastritis in this instance makes it difficult to rule out completely the local origin of the phlegmonous lesion of the stomach (direct route). The chronic gastritis obvious in the microscopic examination represents a preëxisting lesion possibly on the basis of stasis of known cardiac decompensation of many years' duration.

In addition to the three cases described above, which exhibit the classical picture of diffuse phlegmonous gastritis at the autopsy table and under the microscope, we wish to report another case which seems appropriate.

Case 4. Admitted November 29, 1943. Died December 3, 1943. L. S., a two year old white male infant, was admitted with complaints of nausea, vomiting and fever since the morning of admission. Physical examination revealed a comatose child with multiple petechiae. The pharynx and tonsils were slightly injected. The heart sounds were distant. The pulse was barely palpable. The blood pressure was 44 mm. Hg systolic and 32 mm. diastolic. The laboratory data were as follows: 17,800 white cells, 4.9 million red cells, 90 per cent hemoglobin (Sahli), 76 per cent polymorphonuclears, 24 per cent lymphocytes. The spinal fluid showed 8 lymphocytes, no other cells. The urine was positive for albumin.

Course. The child ran a high temperature (to 103.8° F.); the pulse ranged between 130 and 158 per minute. He vomited several times. On the third hospital day he developed nuchal rigidity and a positive Kernig sign. The child died on the fifth hospital day. Blood and spinal fluid cultures before death were positive for meningococcus type 1.

On postmortem examination the stomach (figure 4) appeared moderately enlarged. The serosa was glistening with a slight loss of translucency. On opening along the greater curvature, the stomach wall was found to be diffusely thickened, measuring between 1.2 and 1.4 cm. in width. The mucosa was thrown up into thick folds, in areas covered with mucoid material, and showed multiple minute areas of blood extravasation. On cut section the mucosa itself did not appear to be thicker than usual. In contrast, the submucosa appeared many times the normal thickness. It was sponge-like and porous in appearance in areas, glistening and translucent elsewhere. The muscle also appeared translucent. The swelling of the stomach wall stopped abruptly at the duodenum and somewhat more gradually in the esophageal region.

Microscopic examination of the gastric wall showed edema of the mucosa proper and extensive edema of the submucosa throughout (figure 4a), with wide separation of the supportive tissue and collagen by non-staining and staining fluid. Only a few large mononuclear cells were present in the exudate. In the submucosa, a vessel filling all of the 4 mm. high-power aperture showed a central antemortem thrombus occupying about half the lumen of the vessel.

Giemsa stains failed to reveal any organisms throughout the stomach wall or in the serous exudate. Cocci resembling meningococci were seen within the thrombus described above.

Though not altered grossly, under the microscope the esophagus presented some subepithelial edema towards the gastric end.

The pertinent autopsy findings were an early meningitis and adrenal hemorrhage.

The final anatomical diagnoses were: 1. Septicemia (meningococcus) with

petechiae. 2. Adrenal congestion and hemorrhage (Waterhouse-Friderichsen syndrome). 3. Subserosal edema of stomach. 4. Early meningitis.

Discussion of Case 4: It is our impression that this case represents a first stage of a diffuse phlegmon of the stomach before suppuration and necrosis had set in. This early lesion has been observed in only a few instances, and warrants presentation because of theoretical implications.

FIG. 4. (*Case 4.*) Gross appearance of the stomach. Note edematous, prominent mucosal folds. Central arrow points to minute mucosal hemorrhage. Arrow *A1* points to the duodenum where the edema ends abruptly. Arrow *A2* points to the esophagus, which shows some edema present.

Contini [19] produced marked edema of the submucosa in one of his rabbits by intravenous injection of streptococci. Herrmann [1, 3] and Berka [3] mentioned the fact that in some cases of phlegmonous gastritis the greatly thickened stomach wall can be compressed to normal thickness. This was true in this instance; we could reduce the thickness of the wall by pressure from 1.4 cm. to 0.4 cm. The vomiting, nausea and fever might be considered symptoms of the gastric lesion. The time factor does not favor this interpretation, and these symptoms are all better explained on the basis of the meningococcus sepsis and meningitis.

The *similarity* in the type of exudate seen in the meninges and the stomach is distinctly noteworthy. The positive blood culture and the petechiae on admission, as compared with the appearance of the meningeal signs only on the third day of illness, favor consideration of the meningitis and early gastritis as parallel lesions of later localization. Both sites show only very minimal and similar cell exudate. In passing, we might mention

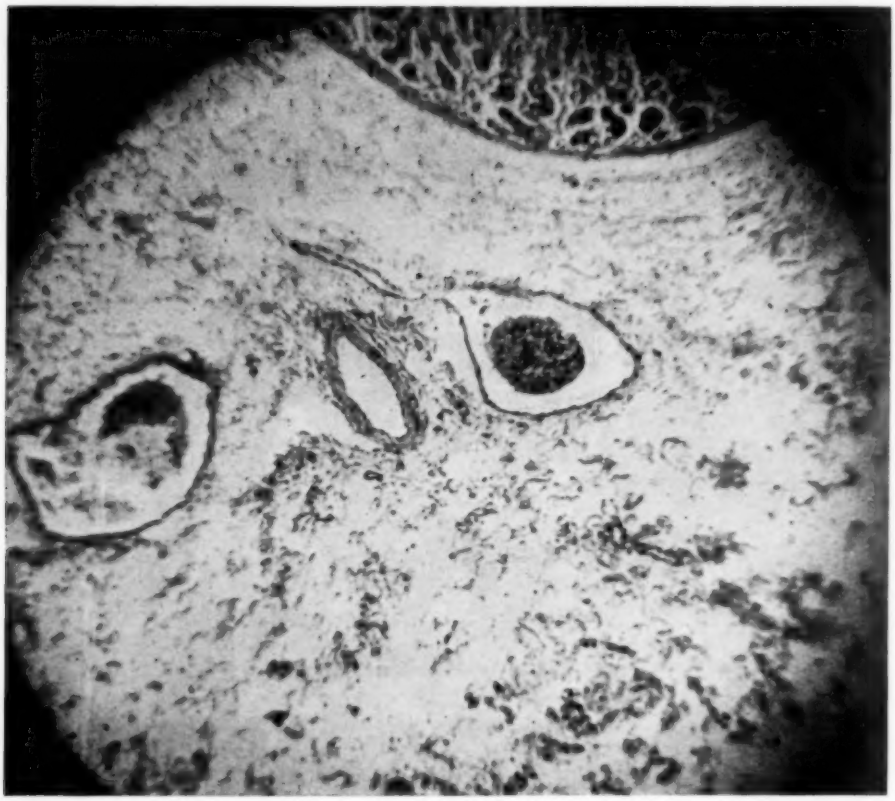


FIG. 4a. (*Case 4.*) L. P. microphotograph showing extensive edema of the submucosa with wide separation of the supportive tissue and collagen by non-staining and some staining fluid. A few large mononuclear cells are present in the exudate. Note thrombus in small venous channel. A small part of the muscularis mucosae and mucosa is included in the photograph.

that to our knowledge no other cases are known in which this condition was produced by the meningococcus.

GENERAL DISCUSSION

In 4,007 autopsies performed at Queens General Hospital from October 1935 to the end of 1943, three cases showed a fully developed picture of phlegmonous gastritis, and a fourth one showed what suggests the earliest

stage of the disease. In none of the patients did a history or physical examination suggest the condition. The diagnosis was not made clinically in any of the cases.

There was no instance of preëxistent mucosal defect such as carcinoma, ulcer, operative wound, etc., which could be considered a portal of entry for invading organisms, suggesting the "direct route" of infection. We believe that in cases 2 and 3 the infection definitely occurred via the blood stream, even though a chronic gastritis was present in the latter. In case 1 the possibility of direct infection by swallowing of organisms cannot be excluded entirely, but the absence of a portal of entry in the stomach mucosa favors the hematogenous route. If case 4 represents the first stage of phlegmonous gastritis, as we assume it does, then it belongs to the hematogenous group.

In contrast to Konjetzny,[3] Gerster,[2] Eliason and Wright [4] and many others it is our opinion that the hematogenous route of infection is the usual one. We wish to compare the process with that occurring in phlegmonous cholecystitis observed in septic conditions. The macroscopic as well as the microscopic picture of gall-bladders in phlegmonous cholecystitis is very similar to that seen in phlegmon of the stomach. The frequent occurrence of cholecystitis, with or without stomach involvement, in Rosenow's [18] experiments is in favor of our concept for the pathogenesis for both entities. Wilkie's [22] experimental production of cholecystitis by streptococcus injections point in the same direction. (See below for discussion of pathogenesis.)

We wish to report for comparison a case of phlegmon of the gall-bladder that illustrates the hematogenous route of infection and resembles closely the above described cases of phlegmonous gastritis.

O. T. Admitted April 28, 1941. Died May 8, 1941. This 25 year old white primipara was admitted to Queens General Hospital because of a sudden rise of blood pressure (144 mm. Hg systolic and 94 mm. diastolic). On admission she was in labor, with ruptured membranes, and a stillbirth was delivered by breech extraction. Her postpartum course was marked by temperature rise, elevation of urea nitrogen from 12 to 160 mg. per cent, creatinine elevation to 6.8 mg. per cent, albuminuria, pyuria, hematuria, and finally anuria. Her white cell count rose to 21,200 with 84 per cent polymorphonuclear leukocytes. The temperature was spiking to 105° F. She lapsed into coma and died the sixth postpartum day.

An antemortem urine culture and blood culture revealed *B. coli.*

At autopsy the gall-bladder was found to be dilated. The lumen contained dark greenish bile. The mucosa was slightly granular, with some focal areas presenting a lighter yellow color. No calculi were found, and no unusual features were seen in the extrahepatic bile ducts.

Microscopically there was marked edema of all layers with extensive inflammatory infiltration. The *mucosa* showed desquamation of most of the epithelial tissue suggesting postmortem autolysis. One area of ulceration was present with bile staining. The ulcer bed extended through the muscular coat and showed destruction of muscle and collagen with extension to the walls of some blood vessels. One vessel just beneath the ulcer bed showed a hyaline thrombus. The *subepithelial*

stroma showed extensive inflammatory infiltration and edema. The underlying *muscle* bundles were widely separated by edema, by compact cellular exudate, or zones of scant inflammatory cell infiltration. Beyond the muscle layer there was distinct edema of the collagen with swelling. There was considerable non-staining edema of the *subserosal* fatty *tissue*. In this coat some perivascular infiltration was present, but the exudate was quite limited in the outermost zones of the external coat.

In the mucosa the inflammatory cells were large mononuclears, some lymphocytes, and a few polymorphonuclear cells. Some large fibroblasts were seen in the exudate. In between the muscle bundles the exudate had a distinct monocytic appearance with some lymphocytes. The serous coat showed only focal accumulation of inflammatory cells with large histiocytes and ordinary monocytes predominant throughout. Giemsa stains revealed small bacilli in the bed of the ulcer described above and in the regional wall.

The final autopsy findings were: 1. Acute bilateral suppurative pyelonephritis with uremia (clinical). 2. Acute cystitis. 3. Sepsis (*B. coli*). 4. Phlegmonous cholecystitis. 5. Purulent bronchitis. 6. Hyperplastic splenitis. 7. Toxic hepatosis. 8. Status postpartum with laceration of vagina and hemorrhage.

Discussion

Infection of the gall-bladder can occur via two avenues, as in the case of infection of the stomach wall. Infection of the contents of the lumen of the gall-bladder can occur obviously by an organism which will not be devitalized by bile. The typhoid salmonella group does match such requirements, and some of our acute and chronic cholecystitis lesions in typhoid may represent infection of the wall from the lumen. The lumen becomes infected by secretion of organisms through the liver as a result of portal circulatory invasion by bacteria. Experimental work demonstrating this has been done with *S. typhi murium*. Yet in some cases of typhoid, cholecystitis has been evidenced by the fact that the wall of the gall-bladder itself contains the organisms when the contents of the gall-bladder fail to do so.

This last situation corresponds to what might be expected on theoretical grounds with the gram positive cocci on the basis of bile action on such organisms, and by the experimental evidence offered by Wilkie [22] and Rosenow [18] and others. Cultural studies of the gall-bladder confirm this finding, for the organism is more readily cultured from the sentinel node or gall-bladder wall than from the bile contents.

It would be natural to expect then that in cases of sepsis where a bacteremic seeding of tissue is possible, the gall-bladder wall might simulate the submucosa of the stomach and become a site for secondary localization of the infection. Of interest in this connection is the controversy still existing in histology as to whether the gall-bladder does represent the equivalent of the coats of the gastrointestinal tract through the submucosa only.

It is our impression that phlegmonous cholecystitis and phlegmonous gastritis have identical mechanisms with a pathogenesis which predicates a general bacteremia with secondary localization in the loose tissue and stroma of the wall of such organs. It is our impression that this is not so rare an

occurrence for both the stomach and the gall-bladder as the current literature would seem to indicate.

Pathogenesis. Many complex classifications of phlegmonous gastritis have been offered. Sundberg [1] separates phlegmonous gastritis into two forms: (a) the form which follows direct implantation of infectious material into the stomach wall, and (b) the form that follows as a result of a metastatic hematogenous process.

There still is a lot of controversy in regard to the pathogenesis of phlegmonous gastritis. In some papers, particularly in the earlier ones, the disease is considered to be metastatic (Brand,[1] Krause,[1] Manoury,[1] Rokitanski,[1] Brinton,[1] Klebs,[1] v. Meyenberg,[3] Dittrich,[11] Lowenstein,[3] Obendorfer,[3] Simmonds,[3] Baird,[3] and Nawerck [3]). The majority of authors stress the direct manner of infection in their cases. Sundberg,[1] in reviewing 215 cases, comes to the conclusion that the metastatic hematogenous type is extremely rare. Konjetzny [3] agrees with him by stating that "proof of this mode of infection is extremely scarce as yet." Gerster [2] and E. Krause [11] are of this same opinion. Rokitanski's [1] conclusion is that, at least in puerperal sepsis, the occurrence by hematogenous route is very rare. Eliason and Wright [4] consider the majority of the cases to occur via "intragastric infection." Bockus [17] states that the disease is either produced by bacteremia or mucosal damage, and so accepts both modes of infection without giving any preferences to one or the other route.

Experimental evidence indicates that both forms of infection exist. Rosenow [18] injected streptococcus cultures into animals in an effort to produce gastric ulcers. In one experiment a rabbit showed at autopsy "what appeared as a phlegmonous gastritis" in addition to cholecystitis, nephritis, endocarditis, etc. Rosenow does not mention the microscopic appearance in this case. In another animal he describes the histological picture of the stomach lesion as follows: "Section through the base of the ulcer showed in the center complete absence of mucous membrane and submucosa, and necrosis of one-third of the circular layer of the muscular coat. There was leukocytic infiltration between the disintegrating epithelial cells, in the submucosa, chiefly around vessels, along the connective tissue stroma, between muscle-bundles and beneath and in the thickened and adherent peritoneal coat." He notes "thrombosed vessels running at right angles to the floor of the ulcer and two large thrombosed vessels in the submucosa" and "marked leukocytic infiltration surrounding the thrombosed vessels in submucosa. Gram-Weigert stains showed a moderate number of diplococci chiefly in the area of leukocytic infiltration and a few in one of the thrombi."

This is the most comprehensive microscopic description we could find in Rosenow's paper. If this is a fairly representative picture of the ulcerative stomach lesions he encountered so often in his experiments, we wonder if he did not deal with a phlegmonous gastritis in many more of his cases. At least the above microscopic picture is almost identical with what we and other authors describe as the classical finding in the stomach phlegmon. This

would imply Rosenow did not produce "the usual ulcer" assuming that he means by this the chronic peptic ulcer of man. The fact that the experimental animal often showed endocarditis, myocarditis, nephritis, cholecystitis, etc., in other words lesions that must be considered manifestations of the hematogenous infection, confirms our concept of the mechanisms involved. Rosenow's work at least in one experiment, and probably in others, demonstrates the metastatic route.

Ashkenazy's [3] paper illustrates the primary or direct manner of producing phlegmonous gastritis. He opened a rabbit stomach at the greater curvature and eroded the mucosa in two areas of the lesser curvature. The curette he used carried material from the floor of a human ulcer that had ruptured. Autopsy after three days revealed an extensive phlegmonous gastritis.

Of interest is another experiment by Doehle, published by Konjetzny.[3] Streptococcus cultures taken from the spleen and the stomach wall of a patient who had died of phlegmonous gastritis were fed to dogs. The dogs remained well. The experiment was repeated after an alcoholic gastritis was produced in the animals. This time the dogs died. Autopsy revealed a streptococcus phlegmon of the stomach with extensive edema and a fibrinopurulent peritonitis.

This experiment bears out the theory of a number of authors who consider gastritis, especially that type which is produced by alcohol, as a predisposing factor for phlegmon of the stomach (Bernstein,[1] Bricheteau,[1] Kinnicut,[1] Wallmann [1]). Sundberg [1] explains this by the fact that gastric mucosa which shows inflammatory changes is extremely vulnerable. According to him these cases of gastritis are in the same category as those in which a defect of the mucosa is present like carcinoma, ulcer, trauma, which acts as a portal of entry for the ingested organisms. Contini [19] produced phlegmons of the stomach by both the local direct and hematogenous routes, using external trauma.

Several other attempts to produce a phlegmonous gastritis were unsuccessful. Symmers [20] fed animals ground glass and inoculated streptococci and pneumococci by way of blood stream or stomach tube without results. Konstantinowich also failed to produce the lesion by feeding glass and streptococci to experimental animals. This might be explained by the fact that ground glass is not a good means of producing a mucosal defect, which is proved by Simmons and von Glahn.[21] These authors failed to produce any lesions whatsoever in dogs by repeated ingestion of ground glass.

Bacteriology. By Gram and Giemsa stain, bacteria are found in all layers of the wall, most numerous, of course, in the submucosa, which is usually the main site of the process. In the center of small abscesses, they often form colonies and little clumps.

Since 1874 it has been known that plegmonous gastritis is produced by bacteria. Heller [1] proved the presence of cocci. In 1885, Sebillon [1] isolated a streptococcus. In Sundberg's [1] cases, 95 were examined bacteriologically. Out of these, 71 cases showed streptococci. Finsterer's [3] statistics

show a still higher percentage; 27 out of 30 cases were positive for streptococci. They were found in pure culture or together with *B. coli* and staphylococci, rarely associated with *B. proteus*. Several cases were produced by pure cultures of pneumococci. Morton and Stabins [10] describe a case due to *B. Welchii*. Also anthrax-like rods, Oppler-Boas bacilli, micrococci, and *B. subtilis* were found by one author. In two patients, Stapelmohr [1] found the pus to be sterile. Both patients recovered. In one of Bircher's [2] cases also the pus was free of organisms. This case died of ruptured splenic varix, a month after successful resection of the phlegmon.

Pathological Anatomy. The difficulty encountered with the clinical diagnosis is not found at the autopsy table. The postmortem findings are very constant and have been recognized for a long time. Cruveilhier [1, 3] gives a detailed autopsy report in 1821 describing "purulent infiltration in the submucosa." This still is considered to be the outstanding and essential lesion. The gross findings vary a little more than do the microscopic. Although most authors describe a great increase in the width of the stomach wall (1 inch in Lehnhoff's [2] case, 8 to 10 centimeters in one of Bircher's [2] cases), a few found a thin wall of only a few millimeters. Hall and Simpson [1, 3] report a case in which the wall was so thickened that in spite of the normal size of the stomach, the cavity was practically obliterated, and the relative size of wall and cavity resembled strikingly that of a uterus. The stomach wall may be firm and rigid, or soft and doughy, or sponge-like. In the latter case, it can be pressed together to normal thickness (Hermann [1, 3] and Berka [3]). The thickening either is diffuse or regional. Walnut-like protrusions into the lumen are described by Hermann in the cases involved regionally. The pyloric area most often shows the severest lesion. Sometimes the phlegmonous inflammation extends to the esophagus (Zenker,[1, 3] Chwostek,[1] Pfister,[1, 3] Schnarrwyler [1, 3]). The duodenum is involved very rarely. Increase in width of the wall is caused mainly by the swelling of the submucosa, whereas grossly the other layers of the wall differ little or not at all from normal.

Symptomatology. Though there exists quite an extensive literature, and the disease has been known for many hundreds of years, phlegmonous gastritis is as yet very rarely diagnosed ante mortem. By going through the published papers, one gets the impression that the correct clinical diagnosis decreases in frequency as time goes on. It seems that phlegmonous gastritis can be diagnosed only by careful history and examination, and that blood chemistry, roentgen-ray, etc., are of little or no value. Berg [5] in "Roentgenuntersuchungen am inneren Relief des Verdauungskanals" points out that "only in very rare instances would phlegmonous gastritis become the subject of roentgen-ray investigation, and only if the course happened to be of more or less subacute character." The authors found very few papers in which roentgen-ray is suggested for diagnosing the ailment (Cutler and Harrison,[6] Watson,[7] Olsson [8]). The last writer states that "extensive thickening of the stomach wall with relatively insignificant changes in the mucosa suggest

phlegmonous gastritis." In Vass and Sirca's [9] case the lesion could not be diagnosed roentgenologically. The symptoms that led some authors to make the correct diagnosis were: very acute onset of complaints such as lack of appetite, headache, nausea, severe abdominal pain either diffuse or localized in the epigastrium and left hypochondrium or even in the right hypochondrium (Barnett and Harris [10]). In rare cases complaints pointing to a stomach ailment were completely absent (André [3] and Cruveilhier,[1, 3] E. Krause,[11] and others). Vomiting is probably the most constant finding of all. The temperature is high from the very onset, being either continuously elevated or septic in character, but is also described as normal or even subnormal (Marshall [12]). The pulse is frequent, weak and irregular. The patient appears severely sick, sometimes excited, apprehensive or lethargic. Hiccough is frequently present.

On palpation of the abdomen severe tenderness and "defense musculaire," especially of the upper abdomen, are noted by many observers. In some cases a tumor-like protrusion in the region of the stomach was found which, according to a few authors, disappeared after vomiting of a purulent material. In reviewing the literature, vomiting of purulent material was not found to be a frequent occurrence by any means. In the vast majority of published cases, no pus was present in the stomach contents. Still rarer is the finding of blood, or of a mixture of blood and pus in the vomitus. Dryness and coating of tongue have been observed rather frequently. In the cases collected by Sundberg, all those studied showed hypoacidity. Icterus, leukocytosis, splenic enlargement, albuminuria, streptococci in the feces, and blood are mentioned in a number of reports.

Of great interest is a symptom which was first described by Deininger [1] in 1879, later mentioned by Kermauner,[1, 3] Bossart,[1, 3] finally by Sundberg,[1] E. Krause,[11] and Cutler and Harrison.[6] They observed that spontaneous abdominal pain disappears on sitting up and reappears on lying down again.

Peritonitis is a frequent feature. Robertson [1] found peritonitis in 70 per cent of his cases, Sundberg [1] in 65 per cent and Jensen [1, 3] in 50 per cent. Pleuritis is much less frequent. According to Lengemann [1] 10 per cent of the patients showed pleural involvement, and according to Sundberg [1] 15 per cent presented this finding.

Whether spontaneous recovery does occur is subject to much discussion. Although the French authors Petit-Dutaillis,[13] Cheinisse,[1, 3] etc., are convinced that cases of diffuse phlegmon of the stomach never get cured spontaneously, Stapelmohr [1] describes a case of spontaneous recovery. Lengemann's,[1] and one of Bircher's [2] patients also recovered. Kaufmann,[1] Bossart,[1, 3] Sundberg [1] and Gerster [2] believe that a spontaneous cure can occur.

That a phlegmonous gastritis can heal by operative intervention has been recently shown in a number of cases (Orator,[2] Novak, Guibal,[2] Brooks and Clinton,[2] Cutler and Harrison,[6] etc.).

From the above it is clear that there is nothing pathognomonic or even characteristic in the signs and symptoms of phlegmonous gastritis. This makes the diagnosis extremely difficult. Few cases are known in the literature in which the diagnosis was made clinically and verified by postmortem examination.

Summary and Conclusion

Three cases of phlegmonous gastritis are presented, showing no mucosal defect in the form of ulcer, neoplasm or operative wound. Marked dilatation of the stomach was an interesting roentgenological observation in one of them.

One case of marked edema of the stomach submucosa in a case of meningococcemia with early meningitis is presented as an early manifestation of a phlegmonous inflammation of the stomach.

Phlegmonous gastritis is compared with phlegmonous cholecystitis. A case demonstrating such phlegmonous inflammation in the gall-bladder wall in a case of known sepsis is presented.

Phlegmonous gastritis is considered a manifestation of sepsis with localization in the stomach wall rather than a lesion following local invasion from the lumen.

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ACUTE PLASMA CELL LEUKEMIA *

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The term "plasma cell" has been applied to a variety of cells since it was first introduced by Waldeyer in 1875.[1] The morphology of the cells was subsequently described in detail by Cajal,[2] Unna,[3] and von Marschalko.[4] These authors presented the characteristics and criteria by which they could be identified. Since these earliest descriptions the literature on these cells has become large and controversial. Papers by Michels [5] and Maximow [6] contain the most complete discussions. The cells are found under normal conditions in the omentum, interstitial tissue of glands, lymph nodes and bone marrow. In pathological states they are found in areas of inflammation (granulomas and perivascular infiltrations) and as new growths.

Under exceptional conditions plasma cells are found in the circulating blood, e.g., measles [7]; Hodgkin's disease [8]; metastatic carcinoma to bones [8]; myeloid leukemia [7]; multiple myeloma [10]; plasma cell leukemia [11]; gonococcus infections [12]; and infectious mononucleosis.[13] The histogenesis of these cells is obscure and they have been variously described as originating from lymphocytes, reticulum cells of lymphoid tissue, adventitial cells of blood vessels and myeloid cells. Jordan [14] strongly advocates the theory that they are abortive erythroblasts. The preponderance of evidence seems to point to the lymphocytes as the probable source of these cells. Naegeli [7] is so convinced of the origin of the plasma cells that he calls them lymphocytes with strongly basophilic cytoplasm. The fate and function of the plasma cell are uncertain, but it has been suggested that they may be converted into connective tissue or back to lymphocytes.

In a consideration of new growths involving plasma cells the solitary extra-medullary plasmacytomas with and without subsequent involvement of distant organs or bone marrow constitute a distinct and separate group. They are most commonly found in the nasopharynx,[15] and to a lesser extent in the conjunctiva, lymph nodes and other sites.[16] These tumors may run either a benign or a malignant course. A recent review by Hellwig [16] brings this entire subject up to date. There is also a small group of cases of single plasma cell tumors originating in the bone marrow. Some of these cases are apparently benign, the patient showing no evidence of disease after extirpation of the tumor.[17, 18, 19, 20] Other cases recur locally or manifest distant metastases.[15]

Multiple myeloma is the most frequent disease involving new growths of plasma cells. The first case of multiple myeloma was described in 1850

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by McIntyre.[21] It was in the urine of this patient that Bence-Jones [22] found a peculiar protein which he reported in 1848. Von Rustizky [23] in 1873 was the first to describe these tumors in detail and to identify the plasmacyte as the invading cell. A complete review of the literature and detailed descriptions of the disease were made by Geschickter and Copeland [24] who reported a total of 425 cases up to that year (1928). In these cases the infiltrating cell was described as a plasma cell. Ulrich [25] in 1939 and Ghormley [26] in 1942 bring the subject up to date and discuss the existence of a specific "myeloma cell" versus the plasma cell. Ewing [15] states that although the tumors generally consist of plasma cells, there are also cases which are made up of myelocytes, lymphocytes and erythroblasts. The classical picture of multiple myeloma is that of a diffuse involvement of ribs, sternum, vertebrae, skull, pelvis and humerus in a neoplastic growth arising in the bone marrow with resulting nodule formation. There are also cases reported in which there is extensive distant organ involvement, but to a lesser extent than is usually seen in leukemia. Included in this group are those cases of multiple myeloma in which plasma cells have been found in the circulating blood. The first case showing this phenomenon was reported by Foa [27] in 1903. Aschoff [28] in 1906 found plasma cells in the blood of a case of multiple myeloma on which he was performing an autopsy. Since these two reports a series of cases has been reported; these cases are recorded in table 1.

Finally there is a small group of cases in which the patients run the clinical course of leukemia showing diffuse organ and bone marrow invasion by plasma cells but no apparent bone marrow nodule formation. In these cases plasma cells were also noted in the circulating blood. Piney [12] described the case of a man, age 48, who complained of weakness in the legs, with pain in the legs and lumbar region. A large spleen was present. An enlarged cervical node was excised and showed an overgrowth of plasma cells. Albumin but no Bence-Jones protein was found in the urine. The white cells varied from 8,400 to 20,000/cu. mm. with 18 to 55 per cent plasma cells. The clinical course of the patient is not given and no skeletal roentgen-rays were taken. At autopsy the spleen was described as enlarged but weighed only 185 gm. The bone marrow of the ribs, upper femur and vertebrae were described as having decreased consistency. The histological sections of liver, spleen, lymph nodes, kidneys and bone marrow showed a widespread invasion of plasma cells, similar to that seen in leukemia. Piney excluded a diagnosis of multiple myeloma because of absence of Bence-Jones protein in urine, the diffuseness of infiltrations in the organs, and the absence of tumor masses in the bones at autopsy. It is difficult for the present authors to accept this case as not being one of probable multiple myeloma. The absence of Bence-Jones protein in the urine is of no consequence as not infrequently it is not found,[29] particularly where hyperproteinemia exists. Furthermore, no roentgen-ray studies were taken during life. The diffuse infiltration of plasma cells in the organs does not militate against a diagnosis

TABLE I

Reported Cases of Multiple Myeloma with Plasma Cells in the Circulating Blood

			Références
Foa	1904	Plasma cells in smears	Folia haemat. Abstracts, 1904, i, 166.
Aschoff	1906	Plasma cells found in post-mortem smears	München. med. Wchnschr., 1906, liii, 337.
Gluzinski and Reichenstein	1906	77% plasma cells	Wien. klin. Wchnschr., 1906, xix, 336.
Luksch	1906	Many plasma cells	Folia haemat., 1906, iii, 325.
Amersbach and Schriddle	1912	Plasma cells in smears	Quoted by VOGT: Frankf. Ztschr. f. Path., 1912, x, 129.
Ghon and Roman	1913	15% plasma cells	Folia haemat., 1913, xv, 72.
Hertz and Mamrot	1913	5% plasma cells	Folia haemat., 1913, xvi, 227.
Beck and McLeary	1919	6.6% plasma cells	Jr. Am. Med. Assoc., 1919, lxxii, 480.
Weinberg and Schwartz	1920	Plasma cells in smears	Virchow's Arch. f. path. Anat. u. Physiol., 1920, ccxxvii, 88.
Wallgren	1920	Case 4–8% plasma cells	Upsala Läkaref. Förh., 1920, xxv, 113.
Piney and Riach	1931	16 to 33% plasma cells	Folia haemat., 1931, xlvi, 37.
Muller and McNaughton	1931	Case 1–39 to 53% plasma cells Case 2–65% plasma cells	Folia haemat., 1931, xlvii, 17.
Cabot Case 21052	1935	5 to 15% plasma cells	New England Jr. Med., 1935, ccxii, 204.
Patek and Castle	1936	12 to 33% plasma cells	Am. Jr. Med. Sci., 1936, cxci, 788.
Jores and Bruns	1936	42% plasma cells	Folia haemat., 1936, lv, 227.
Fleischhacher and Klima	1936	Case 4–0 c.c. plasma cell Case 10–13% plasma cells	Folia haemat., 1936, lvi, 5.
Schilling and Wohlenberg	1938	Few plasma cells	München. med. Wchnschr., 1938, lxxxv, 1292.
Lochnit and Walterskirchen	1939	53 to 71% plasma cells	Wien. klin. Wchnschr., 1939, lii, 67.
Lemaire, Urey, et al.	1940	46% plasma cells	Bull. et mém. Soc. méd. d. hôp. de Paris, 1940, lv, 1366.
Ulrich	1939	0 to 10% plasma cells	Arch. Int. Med., 1939, lxiv, 994.
Rubin	1942	Case 1–38 to 54% plasma cells Case 2–1 to 4% plasma cells	Bull. Hosp. Joint Dis., 1942, iii, 62.
Ashkanazy and Dubois-Ferriere	1942	77 to 93% plasma cells	Helvet. med. acta, 1942, ix, 427.

of multiple myeloma as this disseminated process has been described [15, 24, 25] and is prominently seen in cases listed in table 1.

Jackson, Parker and Bethea [30] (case 5) describe a patient, male adult, age 51, who was admitted to the hospital with the complaints of fatigue, bloating and pain in the legs. The spleen and inguinal nodes were enlarged. There was "moderate elevation" of white blood cells, of which 6.5 per cent were plasma cells. There were also lymphocytes which were difficult to classify. No bone marrow studies or skeletal roentgen-rays were done. Irradiation of the spleen resulted in reduction in the size of this organ. One year later symptoms returned and the spleen again became enlarged. It became smaller following roentgen-ray treatment. "The blood continued to show typical plasma cells and atypical lymphocytes." Eight months later the blood became normal, the spleen remained enlarged and lymphadenopathy was generalized. Biopsy of two inguinal nodes showed no pathological changes. In a discussion of this case the authors state no bone lesions were demonstrated. No subsequent information is available as this patient failed to return for further care.[31] This patient has obviously been inadequately studied and without any follow-up cannot be accepted as a case of plasma cell leukemia. The absence of skeletal roentgen-ray studies and the negative reports of inguinal node biopsies sustain this position.

In 1934 Osgood and Hunter [32] reported the case of a man, aged 49, whose chief complaints were nosebleeds and weakness. The total duration of this patient's illness was six weeks. The patient was markedly anemic. There was hemorrhage from the nose; a gum infection was present; and the breath had a foul odor. The spleen, axillary and inguinal nodes were slightly enlarged. The white cells varied from 15,700 to 34,050 with plasma cells ranging from 47–54 per cent. Bence-Jones protein was absent from the urine. The blood proteins were 8.79 gm.; albumin 1.56, and globulin 6.94 gm. Roentgen-ray studies showed "findings in the skull suggestive of changes found in parathyroid disease. Lues and Paget's disease are also to be considered. The long bones, pelvis and ribs failed to demonstrate any radiographic evidence of pathology." There is no report of any studies on the spine. The patient's course was short in the hospital; during this time he developed petechiae, bleeding gums, epistaxis and otitis media. Autopsy was limited to the abdomen. The liver, spleen and lymph nodes were enlarged and showed widespread infiltrations with plasma cells. The bone marrow was similarly involved. The ribs and sternum were examined with difficulty through the diaphragm and no nodules were felt. The authors excluded a diagnosis of multiple myeloma because of absence of Bence-Jones protein from the urine, absence of bone pain and absence of bone changes. The absence of Bence-Jones protein in the urine has been discussed in the case reported by Piney [12] and is, therefore, of no significance. The authors apparently disregard the roentgen-ray description (quoted above) of the skull, which strongly suggests multiple myeloma. Since the autopsy was limited to the abdomen, tumor nodules might have been present

in the marrow of the ribs or sternum and obscured by a thin layer of cortex. Sections of the skull would have been most desirable before excluding a diagnosis of multiple myeloma.

In 1937 Reiter and Freeman [33] reported the case of a woman, age 66, who complained of weakness and paresthesias of four months' duration. The patient had been treated for six months with liver extract, a diagnosis of pernicious anemia having been made. There was no improvement clinically on this therapy. Physical examination was entirely negative. During the patient's stay in the hospital she manifested great weakness. The total white cells varied from 5,200 to 7,000 with 39 to 48 per cent lymphocytes and 1–8 per cent monocytes. There were no roentgen-rays reported and no diagnosis was given in the paper. At autopsy no skeletal masses were found. No enlarged nodes, spleen or liver were described. The skull was not mentioned. Histological study showed an overgrowth of the lymph nodes, spleen and bone marrow by plasma cells. A differential count was done on the cells in the vessels of the liver and pancreas, and this disclosed 72 to 74 per cent plasma cells. The authors concluded that the blood smears during life were misinterpreted and that the so-called lymphocytes were most probably plasma cells. The same criticism must be applied to this case as was mentioned in those described by Piney [12] and by Jackson,[30] since no roentgen-ray studies were made during life.

The cases listed in table 1 are obvious cases of multiple myeloma with plasma cells in the peripheral blood. The second group described in detail (Piney, Jackson et al., Osgood and Hunter, Reiter and Freeman) probably fall into the same group for the reasons listed in the description of each case. The present authors therefore present the following case which they feel fulfills all the criteria of an acute leukemia.

TABLE II

Cases Reported as Plasma Cell Leukemia

Piney [12]	1924	18 to 55% plasma cells
Jackson, Parker and Bethea [25]	1931	6.5% plasma cells
Osgood and Hunter [23]	1934	47 to 54% plasma cells
Reiter and Freeman [34]	1937	72 to 74% plasma cells

CASE REPORT

W. B., white female, age 67, was admitted to the Kings County Hospital on April 30, 1943, with the chief complaints of pain across the chest and swelling of feet and legs. Patient had dropsy at the age of six and since she was 35 years of age there were numerous attacks of dependent edema and dyspnea. For four weeks prior to admission the patient had had severe frontal headaches, dizziness and periods of unconsciousness. During this period she lost nine pounds and occasionally coughed up a little blood. The positive physical findings on examination were the apparent severe anemia, ptosis of the left eyelid, enlarged cervical and inguinal nodes, and the presence of a round mass in the right iliac region which was movable and painful on pressure. Temperature was 100.2° F.; pulse 100; blood pressure 120 mm. Hg systolic and 60 mm. diastolic. Urinalysis disclosed albumin 3 plus with many hyaline casts and white blood cells. The initial and subsequent blood counts are shown in table 3.

TABLE III

Peripheral Blood

Date	Hb	RBC	WBC	Seg. PMN	Non-Seg. PMN	Myelocytes	Lymphocytes	Monocytes	Plasma Cells
5/6/43	55%	2,140,000	31,000	30%	6%	2%	11%	7%	44%
5/11/43	50%	2,450,000	15,000	49%	31%	4%	11%		5%
5/13/43			11,000	64%	11%		9%	13%	3%

Further laboratory examination made during the first 48 hours in the hospital showed: Urea 58 mg. per cent; sugar 82 mg. per cent; creatinine 1.4 mg. per cent. Prothrombin time was 75 per cent of normal. Urinary urobilinogen was 4 plus. Bence-Jones protein was absent from the urine. The total proteins of the blood were found to be 11.0 gm. per cent of which 2.5 gm. were albumin and 8.5 gm. globulin. Blood Wassermann reaction was negative. Sternal puncture was done on several occasions and the results are noted in table 4.[34] Three days after admission the

TABLE IV

Bone Marrow Studies

Date	Total Nucleated Cells	Megakaryocytes	Seg. PMN	Non-Seg. PMN	Myelocytes	Myeloblasts	Plasma Cells	Lymphocytes	Megaloblasts	Erythroblasts	Normoblasts
5/6/43	32,000	0	27%	7%	6%	0	48%	8%	0	0	4%
5/8/43	45,000	0	7%	4%	8%	1%	27%	4%	0	0	49%
5/11/43	250,000	22	13%	8%	6%	0	30%	4%	0	1%	38%
5/13/43	175,000	0	4%	5%	16%	1%	31%	3%	1%	3%	36%

patient developed signs of bronchopneumonia at both bases and sulfathiazole therapy was instituted. The highest blood level reached was 3.8 mg. per cent. During the entire course in the hospital the patient was drowsy and slept most of the time. A lumbar puncture five days after admission revealed no abnormalities. On the sixth day the patient complained of pain in the abdomen and passed a yellow watery stool. She was obviously icteric. The gums were oozing and swollen. Purpuric spots were found over the body. The axillary nodes were now enlarged in addition to the cervical and inguinal. The signs of consolidation became more marked at the right base. This was confirmed on roentgen-ray of the chest. The patient was given three transfusions of 500 c.c. each, but died 18 days after admission to the hospital. Complete skeletal roentgen-rays were taken but no abnormal bone changes were found.

The cells designated as plasma cells in the peripheral blood and bone marrow were of several types. Many were typical, being slightly larger than the lymphocyte, having a deep blue cytoplasm with a clear zone opposite the eccentrically placed nucleus. Some of the nuclei had the typical cartwheel structure; others showed a thick dense irregular chromatin (figure 1). There were other cells which were slightly larger, the cytoplasm varying from pink to bluish-gray, and a slightly larger nucleus also eccentrically placed. These cells resembled atypical normoblasts and erythroblasts. The nuclei of these cells resembled those of the typical plasma cell (figures 3 a and b). Finally there were some cells which were two to three times the size of the usual lymphocytes. The nuclei of these cells were large, occasionally oval but usually round, and finely granular. One to three nucleoli were present. The cytoplasm was of a deep blue color and had a thin clear peri-nuclear zone. These

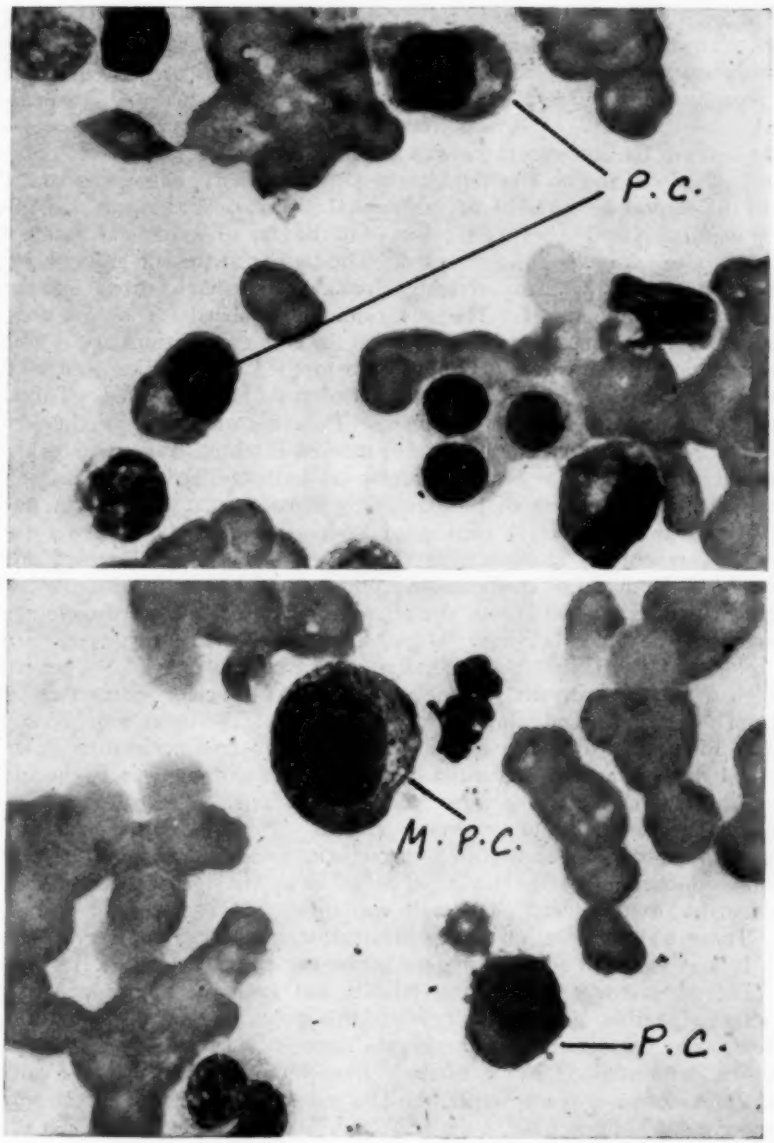


FIG. 1. (*above*) Antemortem bone marrow smear showing typical plasma cells (P.C.). × 1000.
FIG. 2. (*below*) Megaloblastic type of plasma cell (M.P.C.). × 1000.

cells were interpreted as being immature plasma cells and resembling closely megaloblasts (figure 2).

Autopsy. Description: The body was that of a well developed, poorly nourished elderly adult female, 5 feet 2 inches in height and weighing about 120 pounds. In the left cervical region there was a hard mass, about the size of a lemon. There was bilateral axillary and deep inguinal adenopathy, the nodes being discrete, and about

the size of walnuts. The body was waxy-white in color. There were varicosities of both legs. There was dependent lividity, with no jaundice, edema or operative scars, and no external evidence of recent injury. There was normal hair distribution and normal postmenopausal external genitalia. *Incision:* The usual "Y" shaped incision was made, and the sternal plate was lifted in the usual manner. *Body cavities:* Immediately beneath the sternum there was a large antemortem blood clot. There were no pleural adhesions, and no free fluid in the pleural cavity. There was no abdominal fluid, and the serosal surfaces of the abdominal viscera were smooth and glistening. The deep inguinal lymph nodes were enlarged to the size of walnuts and were discrete. *Head:* The scalp was incised and reflected. The tissues of the sub-galea were slightly edematous, and presented many roughly circular hemorrhagic areas measuring approximately 4 mm. in diameter. The calvarium was removed. The dura was slightly adherent, especially along the sagittal sinus. Several granulations were noted here. Transillumination of the calvarium showed no rarefied areas. The dura was incised and the brain exposed. Marked subarachnoid edema fluid was noted. This occupied the convex surface of the entire hemisphere. Puncture of the pia-arachnoid released considerable fluid. There was moderate to marked cerebral atrophy, as evidenced by widened and deep sulci. The brain was removed and examined. No areas of softening were noted. The vessels of the base were normally constituted, but the site of marked atherosclerosis. Serial section of midportion showed no gross pathologic lesion of the cerebellum. Horizontal section of both hemispheres revealed small cysts, which occupied the nuclei of the base. No other abnormality was visualized. *Lungs:* The right lung weighed 660 grams, the left lung 650 grams. There were small hard white areas in the apices of both lungs. The surfaces of both lungs were gray-blue in color, and they both had increased resistance centrally, while the periphery was spongy. Cut surfaces revealed the lungs to be gray in color, edematous, and well aerated. There was marked hilar adenopathy. *Heart:* The heart weighed 260 grams. It lay free in the pericardial cavity, and there was no free pericardial fluid. There was normal distribution of epicardial fat. The myocardium was of normal thickness, but the papillary muscles were moderately effaced. The valve surfaces were smooth, and chordae tendineae were not thickened. The ostia of the coronary arteries were patent; the vessels were traced throughout their course, and showed no obstruction or thickening of the walls. The aorta showed generalized, raised yellow plaques and had some ulcers. The wall was thin. The ostia of all branches were patent. There was calcification at the bifurcation. *Liver:* The liver weighed 2,030 grams. It was enlarged to four fingers below the costal margin. The edges were sharp. The surface was smooth and friable, and gave the appearance of red and yellow streaked marble. Cut section revealed this streaking to stand out more markedly, the yellow being homogeneous. The hepatic vessels and ducts were grossly normal. The gall-bladder contained 20 c.c. of dark green bile. Two small black calculi were present. The mucosa was thickened; the bile ducts were patent; and pressure on the gall-bladder caused bile to flow at the ampulla of Vater. *Spleen:* The spleen was enlarged and weighed 600 grams. It was soft and boggy. Several hard areas were palpable. It was grayish-red in color. The cut surfaces were boggy, and showed an increase in the gray pulp. There were black nodules present, which corresponded to the hard areas felt on the surface. *Adrenals:* The adrenals were normal in position and size. Their surfaces were yellow, and cut sections revealed a yellow cortex and brown liquefied medulla. *Kidneys:* The kidneys were small, and will be described together. Each weighed 160 grams. The surfaces were maroon in color, firm in consistency, and smooth in texture. The capsules were stripped with ease. Cut surfaces revealed cortex and medulla to be well demarcated, and the normal relationship existing between the two. The calyces, pelves and ureters showed no gross abnormality. The bladder contained 80 c.c. of cloudy yellow urine. The trabeculae

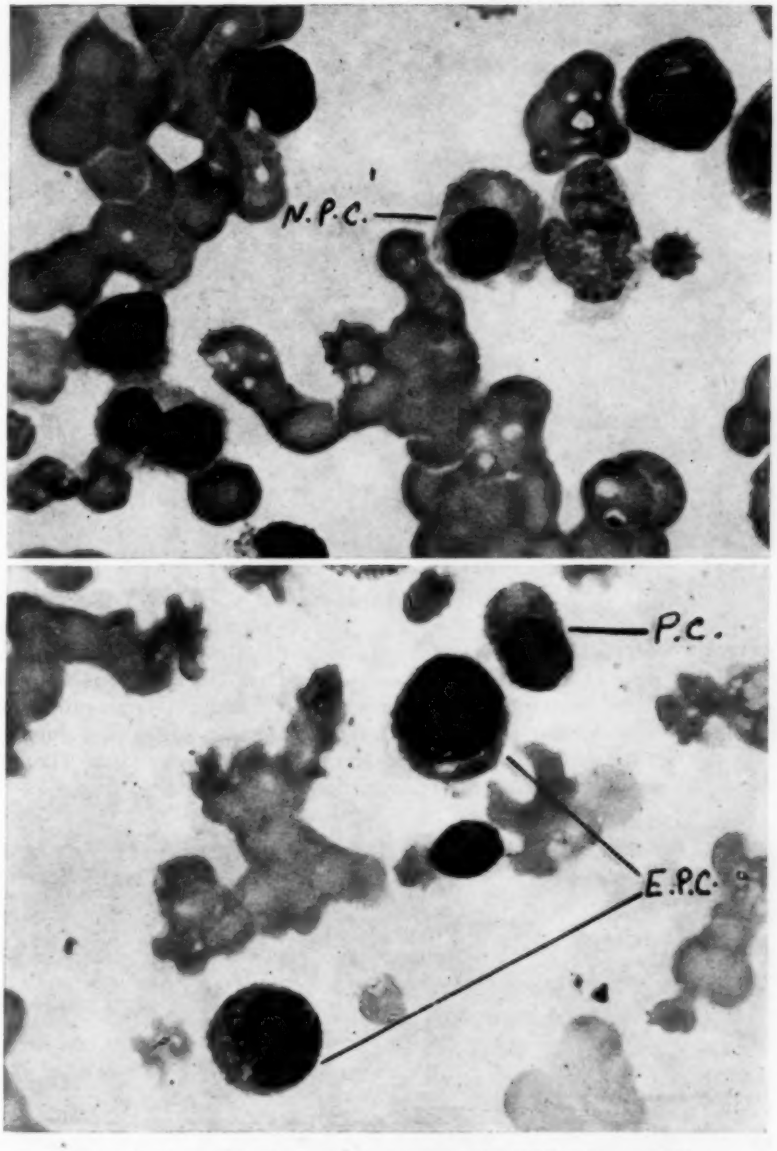


FIG. 3a. (*above*) Normoblastic type of plasma cells (N.P.C.). × 1000.
FIG. 3b. (*below*) Erythroblastic type of plasma cell (E.P.C.). × 1000.

were normal in size, and the mucosa was injected. *Genitalia:* The ovaries were atrophic. The tubes were patent, and their fimbriated ends lay free in the abdominal cavity. The uterus was small and hard. The cervical canal was patent and its mucosa showed no gross abnormality. The mucosa of the fundus was dark red in color. There were no new growths that stood out from the surface of the mucosa. *G. I. Tract:* The esophagus showed no dilatation, varices, or diverticulum. The mucosa was smooth and black in color, probably from postmortem autolysis. The stomach contained 100 c.c. of light green fluid. The mucosa was injected and the

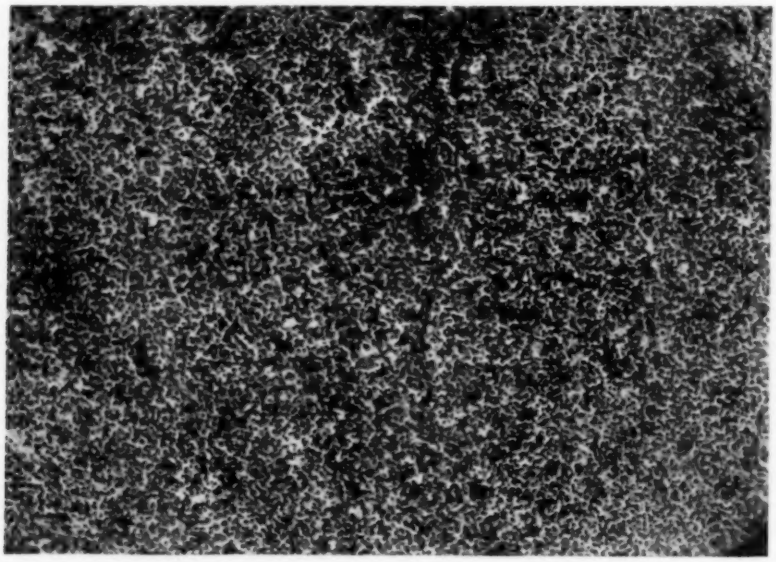


FIG. 4. Spleen. × 120.

rugae were atrophic. There was no ulceration or growths. The duodenum, jejunum and ileum were empty. The mucosa was injected, but there was no ulceration. There was generalized mesenteric adenopathy. There were no mesenteric thrombi or hemorrhage. The cecum, ascending, transverse, descending and sigmoid colons showed no obstruction or diverticula. The rectum was full of feces. The appendix was present and showed no gross evidence of disease.

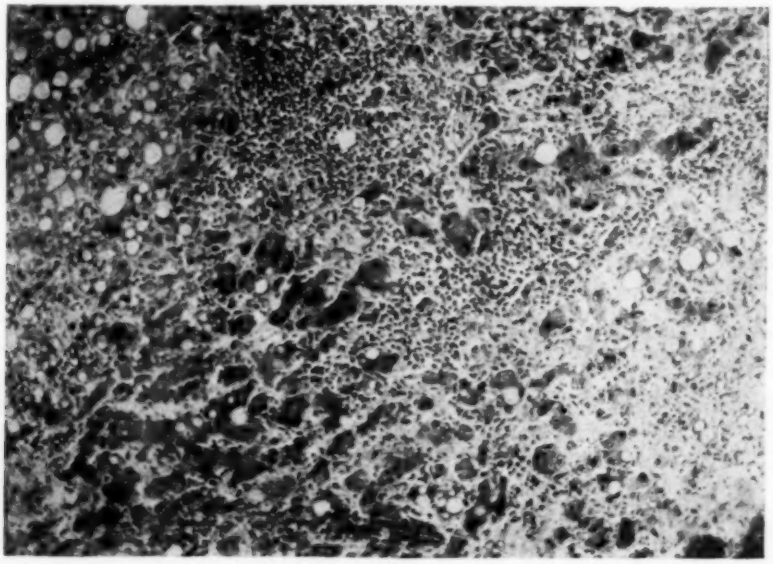


FIG. 5. Liver. × 120.

Microscopic Study: (Interpretation by Dr. W. W. Hala). *Spleen:* There was a diffuse infiltration of plasma cells into the sinusoids, mixed in with the pulp cells. There were no discrete aggregations of plasma cells. The Malpighian corpuscles were indistinct and obscured. Another section of the spleen disclosed an area of hemorrhagic infarction. *Bone Marrow:* Hyperplastic with an apparent increase of plasma cells. *Liver:* There was an infiltration into the portal spaces and sinuses consisting of round, plasma and reticuloendothelial cells. The parenchymal cells showed evidence of extensive fatty changes (figure 5). *Lymph node:* No follicles were present. The normal architecture was completely destroyed and was replaced by an overgrowth of small round and plasma cells which had infiltrated into the surrounding fat (figure 6). Imprints made of an inguinal node immediately after death demonstrated nests of plasma cells more distinctly. Most of these were typical

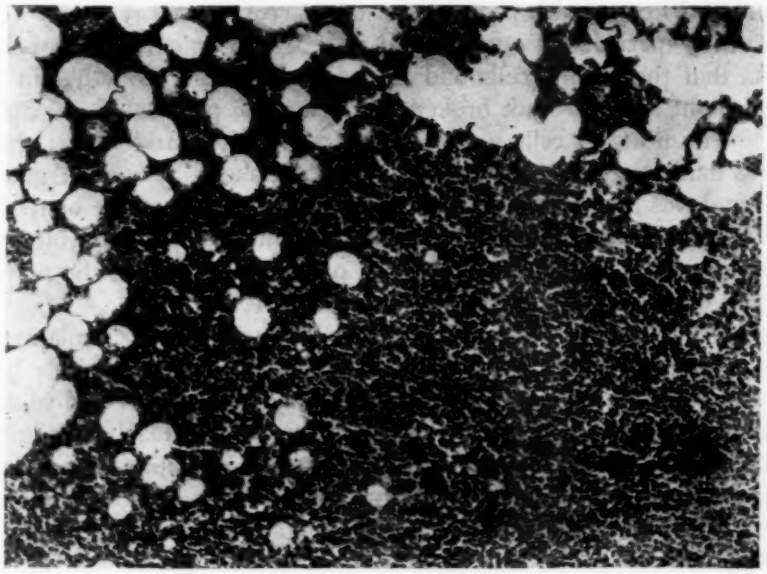


FIG. 6. Lymph node. × 120.

plasma cells, but a few resembled normoblasts as found in the peripheral blood. The preponderance of cells, however, were lymphocytes. There was no evidence of infiltration into any of the other organs, the only pathological changes being the usual degenerative ones which are associated with senility.

DISCUSSION

The authors do not wish to enter into the controversy as to the origin of the plasma cell. However, from the material at hand in this case, the erythroblastic theory of Jordan [14] finds great favor. In initial cursory examination of the marrow smears many of the cells were thought to be "atypical" megaloblasts and erythroblasts. The staining qualities of the more immature cells strongly suggested the former, and it was only after examination of many fields that the true nature of these cells was determined. Many of the older plasma cells strongly resembled normoblasts with cyto-

plasm which appeared hemoglobiniferous. At the same time the authors are aware of the overwhelming weight of such experiments as those of Maximow [9] who demonstrated the growth of plasma cells from lymphocytes after two days' incubation. However, the issue does become more complicated if one bears in mind the reports of Furth [35] who found that the intravenous injection of myeloid cells into mice produced in some instances myeloid leukemia and in other animals multiple myeloma.

The present authors have utilized the method of sternal puncture in all cases showing hematologic disorders and have found the marrow to be diffusely involved in all cases of multiple myeloma. This is in accord with the findings of Rosenthal and Vogel.[36] Beizer, Hall and Griffin [37] found only eight out of 10 cases with positive sternal marrow punctures. However, it has been the experience of one of us (L. M. M.) in an early case of multiple myeloma that the plasma cells had a tendency to clump together in groups of six to eight and were not broken up during the process of preparing the smears. The nests of cells were so characteristic when seen that the diagnosis was made even though the smears did not show diffuse overgrowth of the cells and was later confirmed on roentgen-ray studies of the bones. This suggests that with the greater use of sternal puncture as a routine measure in obscure cases, particularly of anemias of unknown origin, the number of recognized cases of multiple myeloma will increase.

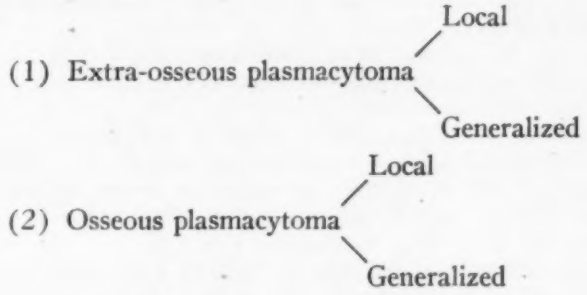
The cases of multiple myeloma with plasma cells in the circulating blood bear a strong analogy to patients with lymphosarcoma who show lymphosarcoma cells in the peripheral blood, as reported by Isaacs,[38] and to cases of leukosarcoma originally described by Sternberg.[39] Similarly, patients with lymphatic and myelogenous leukemia often show asymptomatic single and multiple localized bone lesions if routine roentgen-ray studies are done.[40, 41] Another close analogy is to cases of chloroma where both intra- and extraosseous green tumors occur in conjunction with the blood picture of leukemia.

Another interesting associated finding was the elevated blood proteins with the globulin reaching a level of 8.5 grams per 100 c.c. of blood. This neither militates against nor confirms the diagnosis of multiple myeloma or plasma cell leukemia since hyperproteinemia is present in other diseases (notably cirrhosis of liver, lymphogranuloma venereum and kala-azar [42] and may be absent in myelomatous disease (especially where Bence-Jones protein is found in the urine [29]).

As far back as 1907 Pappenheim [43] suggested that multiple myeloma is a generalized disease of the hematopoietic tissue which happens to affect at first or primarily the bone marrow. Since that date numerous authors have stressed the relationship of diffuse multiple myeloma to the lymphatic and myelogenous leukemias. This becomes even more apparent when patients with diffuse myelomatous tumors begin to show plasma (myeloma?) cells in the circulating blood, as recorded in table 1. The present case reported completes the chain in the analogy to lymphoid tumors in that no masses

were demonstrated in any bone either by complete skeletal roentgen-rays or after a careful search at the autopsy table. The diffuse invasion of organs, including lymph nodes and bone marrow with the presence of immature and mature plasma cells in the circulating blood justifies the designation in this case of acute plasma cell leukemia.

The classification of tumors involving plasma cells which has been suggested by several authors (Naegeli,[7] Jackson et al.,[30] Muller and McNaughton (table 1), and Ulrich[25]) may be combined into the following simple but comprehensive form:



Summary and Conclusion

1. A case of acute plasma cell leukemia is presented which fulfills all the clinical and hematological criteria necessary for the diagnosis of acute leukemia.

2. The elevated blood globulin in association with overgrowth of plasma cells in organs, bone marrow and peripheral blood indicates the close relationship of this case to diffuse multiple myelomatosis.

3. A review of the literature of various plasma cell neoplasms suggests that they are all part of the same disease process involving hematopoietic tissues and organs. The above case completes this chain.

4. A condensed and comprehensive outline of plasma cell tumors is presented.

5. From the material at hand in this case it is suggested that some plasma cells are developed from abortive megaloblasts or their derivatives.

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CASE REPORTS

AN UNUSUAL CASE OF AORTIC ANEURYSM*

By S. P. Sanford, M.D., *Savannah, Georgia*

On October 13, 1939, a negro male, age 18, who gave the date of his birth as June 3, 1921, was admitted to the hospital with primary syphilis. His history revealed that his father, age 45, was living and well, and that his mother died at the age of 30, cause unknown. Four siblings are living and well. The patient was single. He had had measles in childhood, mumps at eight, chickenpox at 10, and malarial fever at 13.

His present illness had begun about three weeks before admission with a penile ulcer and generalized pustular eruption over the body. There was no itching. There had been no noticeable loss of appetite. There had been a feeling of feverishness intermittently for two weeks.

Physical examination revealed a young negro male with good musculature. There was a healing ulcer in the coronal sulcus that was definitely indurated. The epitrochlear and inguinal lymph nodes were definitely enlarged. One inguinal node was rather large and painful. The body was covered by numerous pustules. The rest of his physical examination was normal.

A dark-field examination of the ulcer showed spirochetes of syphilis. The Wassermann reaction was strongly positive, and the Kahn reaction was strongly positive, 240 units. The blood examination was as follows: red blood corpuscles, 3,800,000; white blood corpuscles, 5,000; hemoglobin, 50 per cent; differential count: small mononuclears 26 per cent, large mononuclears 1 per cent, and neutrophiles 73 per cent. Feces showed ova of *Trichuris trichiura*.

The patient was treated with neosalvarsan, 0.3 gram initial dose, followed at weekly intervals by 0.6 gram for eight doses. He was also given concurrently eight doses of thio-bismol 0.2 gram each. A spinal fluid examination was made on October 25, which was reported as follows: Albumin normal. Cell count 1. Globulin negative. Mastic 000000. The intestinal parasites were apparently removed by tetraethylene M60 successfully as subsequent examination showed no ova.

The serological tests for syphilis made at the conclusion of the first course of treatment were as follows: Wassermann reaction, four plus. Kahn reaction, four plus; units 10. The patient did not return for a second course.

On July 24, 1941, approximately two years after initial infection, the patient returned to this hospital complaining of severe pains over his heart. These, he stated, had begun three weeks previously while he was employed as a shrimp fisherman. He had had paroxysmal nocturnal dyspnea. He had had a slight fever for six weeks, but no other symptoms were elicited on careful questioning.

Physical examination at this time revealed a well developed muscular negro male of 20 years, weight 138 pounds, height 5 feet, 6 inches.

The pupils were small, equal and active. The alignment and development of the teeth were excellent; the throat was normal. The neck showed marked pulsations in both carotid regions and in the region of the right subclavian artery. The thorax was well covered, and there were no other pulsations noted by direct and tangential inspection. The heart rate was 90 and the rhythm regular. The apex impulse was

* Received for publication July 26, 1943.
From the Medical Service, U. S. Marine Hospital, Savannah, Georgia.

not sharply localized. The sounds were overactive. The aortic second sound was accentuated, low pitched and followed immediately by a murmur. His blood pressure was 120 mm. Hg systolic and 60 mm. diastolic, the same in both arms. The aorta was easily felt in the jugular notch. The peripheral arteries were not sclerosed, and there were no varicosities. Duroziez's sign was not elicited. The lungs were clear. The abdomen was negative. The spleen was not palpable. The cervical, axillary, epitrochlear, and inguinal lymph nodes were all palpable. The urinalysis was normal; the red blood count was 4,270,000; hemoglobin, 69 per cent. The Wassermann and Kahn tests were negative. The spinal fluid examination of August 5, 1941, was as follows: Albumin normal. Globulin negative. Cell count 8 cells per cu. mm. fluid. Mastic 000000. C. S. F. Wassermann reaction—negative.

A roentgenographic examination of the chest revealed a large aneurysm of the distal portion of the aortic arch. A simultaneous electrocardiogram and stethogram

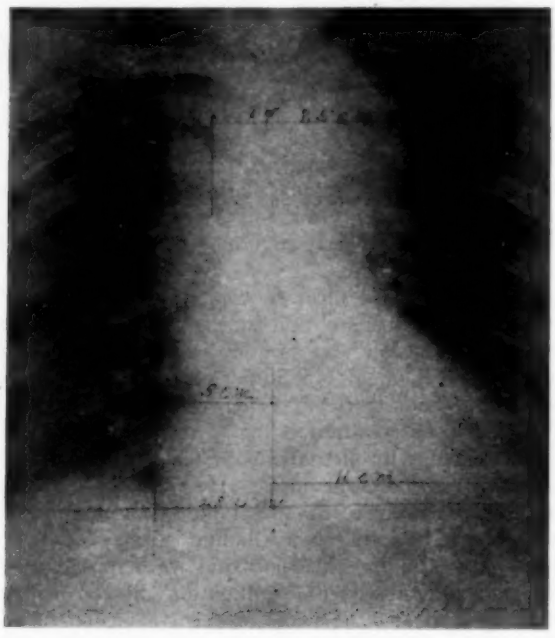

FIG. 1. Roentgenogram of chest taken July 24, 1941, showing aneurysm.

showed a diastolic murmur replacing the second sound. The conducting mechanism was within normal limits, S_1–S_2 and S_3 were slurred.

A second roentgenographic examination of the aorta showed the ascending loop reduced in size. This was thought to be caused by subsidence of perivascular lymphedema. It does not seem reasonable to believe that the reduction in size represents a reduction in the caliber of the aorta.

The patient lived until December 5, 1942, when he finally succumbed to pulmonary congestion. Peripheral signs of aortic insufficiency had developed.

An autopsy revealed a saccular aneurysm almost four inches in diameter below the descending loop of the arch. The aortic valves were eroded. The rest of the thoracic aorta was involved in a syphilitic process of thickening and longitudinal striations.

In negro patients aneurysm of the aorta has not been an infrequent finding. The average age at the onset of the symptoms is considerably lower than that

for the general population. This has been attributed to widespread youthful infection and to arduous labor. It is not unusual to see negroes incapacitated by aneurysms or other forms of vascular syphilis in the early thirties, but for aneurysm to develop in a 20 year old youth, within two years of the proved initial infection, is indeed a medical curiosity.

Evans [2] was able to find only two cases of thoracic aneurysm in persons below the age of 30 in addition to one case which he reported. One of these cases was 29 and the other 28.

In this period of 46 years there were 840 cases of thoracic aneurysm admitted to the London Hospital.

SUMMARY

This case of a 20 year old negro dying from an aneurysm of the aorta is unique from two standpoints. In the first place aneurysm of the aorta is extremely rare in one so young. In the second place it is very rare for an aneurysm to develop within two years of proved primary infection.

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DISSEMINATED VISCERAL IDIOPATHIC HEMORRHAGIC SARCOMA (KAPOSI'S DISEASE): REPORT OF CASE WITH NECROPSY FINDINGS*

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THE lesion of idiopathic hemorrhagic sarcoma (sometimes called angioreticuloendothelioma) or Kaposi's disease, is a granulomatous tumor characterized by vascular proliferation and hyperplasia of spindle cells which are of doubtful origin.[1, 2, 3, 4] The fact that various theories have been advanced as to the pathogenesis of the disease is indicative of the fact that the actual nature of its origin remains obscure, although it is generally believed to represent a true neoplastic process rather than an infectious one.[2, 4] The disease occurs almost always in men who are manual laborers, the great majority of them being Jewish or Italian, of eastern European or northern Italian stock [1, 4] usually during the fifth, sixth or seventh decades of life. The course of the disease is ordinarily prolonged, lasting from six months to 25 years.

Visceral involvement associated with cutaneous lesions in Kaposi's disease is not uncommon. Disseminated visceral lesions in the absence of cutaneous manifestations is relatively unusual and, in fact, the existence of such substantiated cases has been strongly questioned.[1] In an extensive review of the subject

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Choisser and Ramsey [4] cited one instance of Kaposi's disease without skin lesions and reported two additional cases. Weller [5] has also described two similar cases. The purpose of this communication is to present the clinical study and necropsy findings of a patient who had no skin manifestations but who showed widespread visceral involvement by a hemorrhagic sarcoma the histological picture of which conformed to the accepted descriptions of the lesion of Kaposi's disease.[1, 2, 3, 4] A point of interest in this instance in addition to the lack of skin lesions is that the brain and thyroid contained foci of the tumor. It has been stated [4] that no case of Kaposi's disease has been reported to have had involvement of these organs and we have been unable to find such a description. There was also cardiac involvement with the formation of an auricular thrombus. Involvement of the heart has been reported in eight cases of Kaposi's disease.[4, 5]

Case Report

The patient was a 59 year old white American born tool-maker whose parents also had been born in this country. He was admitted to the hospital because of weakness of the left arm and leg of two and one half weeks' duration. The family history was irrelevant. The patient's past history is significant in that he had been admitted to the hospital one year previously because of left upper lobe lobar pneumonia due to pneumococcus type III, which responded well to sulfadiazine. He was also digitalized because of slight cardiac enlargement, auricular fibrillation and evidence of some pulmonary congestion. However, at the time of his discharge one month after admission, roentgenographic examination of the chest still showed consolidation of the left upper lobe as well as a coarse mottling throughout the entire right lung field which earlier had presented the appearance of passive congestion but which now had assumed a more nodular appearance. He was advised to return for complete reexamination after a period of convalescence but this he failed to do. From that time until his terminal illness he felt perfectly well, continued at his work, and he presented no referable complaint including respiratory distress, chest pain, cough, hemoptysis, sputum, and there was no weakness or loss of weight. Upon returning home from work two and one half weeks before his next and last hospital admission he had suddenly been seized by uncontrollable spasmodic flexion movements of his left arm and leg. There was no aura, he did not lose consciousness, nor was there urinary or fecal incontinence. He had never experienced such an episode previously. The jerking movements of the extremities subsided in about 15 minutes, but he then discovered marked weakness of these members which persisted so that he had been unable to return to his work. Five days before coming to the hospital, while walking, his left foot had caught beneath a rug, causing him to fall to the floor striking his head and left lower back. A small laceration was produced over the occiput and left him with persistent severe pain about the left sacroiliac region which caused him to come to the hospital. For approximately a year, about once a month he had been experiencing biparietal headaches each of which lasted only for a few hours and which had not been of sufficient severity to cause him to seek medical attention.

Physical examination revealed a well-nourished and well-developed man who did not appear to be chronically ill nor in any acute distress. He was completely conscious, coöperative and well-oriented. Rectal temperature was 100° F., the pulse rate was 105, respirations 22. The systolic blood pressure was 140 mm. of mercury and the diastolic 90 mm. of mercury. There was no pallor or cyanosis. The skin was not pigmented nor did it present the appearance of any unusual lesions. The pupils were round, regular and reacted normally to light and to accommodation. The ocular fundi showed only evidence of moderate arteriosclerotic changes. The brachial and

radial arteries were somewhat thickened but were not tortuous. Pulsations were present in the vessels of the lower extremities. The heart was moderately enlarged to the left, the apex being in the fifth interspace 10 cm. left of the midsternal line. The cardiac rhythm was totally irregular, and there was a pulse deficit of 20. A soft systolic murmur was audible over the lower sternum. The lung fields were resonant throughout; vocal and tactile fremitus were within normal limits; the breath sounds were everywhere vesicular in nature, and medium moist crackling râles as well as an occasional sibilant râle were heard over both lung fields posteriorly. The abdomen was soft; there was no tenderness and no mass. Enlarged organs could not be palpated. Rectal examination was negative apart from a moderately and symmetrically enlarged prostate of normal consistency. There was no unusual adenopathy. The thyroid was of normal size, shape and consistency. The genitalia were normal and there was no palpable mass in or about the testicles. There was moderate weakness of the left hand and arm but marked weakness of the left leg. All of the deep reflexes of the left upper and lower extremities were increased although there was no clonus. The left Babinski test was positive; the Sheldon and Hoffman tests were negative. There was no sensory disturbance and vibratory and position sense remained intact. The left abdominal reflexes were diminished and the left cremasteric reflex was absent. The cranial nerves were intact.

Laboratory Data. The red blood cells numbered 4.89 million, the hemoglobin was 14 grams per 100 c.c. of blood. The white blood cell count, differential count and blood smear were not unusual. The urine contained no albumin, sugar, acetone or cells, and the specific gravity was 1.024. Routine flocculation tests for syphilis were negative. The stool examinations were negative for occult blood. Lumbar puncture was performed. The initial pressure was 100 mm. of water, the final pressure 80 mm. of water after removal of 8 c.c of fluid; the dynamics were normal. The cerebrospinal fluid was clear, contained 3 lymphocytes and 12 fresh red blood cells. The Pandy test was 3 +, protein content of initial fluid was 70 mg. per 100 c.c. and of the final fluid was 68.3 mg. per 100 c.c. Electroencephalography revealed abnormalities which were most marked over the right central area. The Ascheim-Zondek test was negative.

Roentgenographic examination of the skull, the sacroiliac region, flat plate of the abdomen, and intravenous pyelography revealed no abnormalities. Examination of the chest, including laminography and Bucky films, revealed numerous nodules throughout both lung fields which were characterized by radiopacity and which were rounded in appearance with indistinct borders. The interpretation was carcinomatosis of both lungs but whether this was primary carcinoma of the lungs or metastatic from without could not be ascertained from an examination of the films. The patient's general condition did not warrant a gastrointestinal series.

The day following his hospital admission, while being examined, there was noticed the sudden onset of jerking twitching movements of the muscles over the left upper abdomen at a rate of 30–40 per minute, which lasted about one and one-half minutes. On the thirteenth day he seemed somewhat clouded mentally and although he remained well-oriented his behavior seemed peculiar. On one occasion he vomited a small amount of fresh blood. Despite supportive measures his general condition became progressively worse. On the nineteenth day he lapsed into deep coma from which he never could be aroused, and he died on the twenty-fifth day. The clinical impressions were: arteriosclerotic cardiovascular disease, auricular fibrillation, compensated; pulmonary carcinomatosis, primary site not established; the nature of the central nervous system lesion remained obscure but might be attributed to metastatic cerebral neoplasm, cerebral embolus from an auricular mural thrombus or possibly cerebral thrombosis.

Necropsy. The body was that of a well-developed and fairly well-nourished

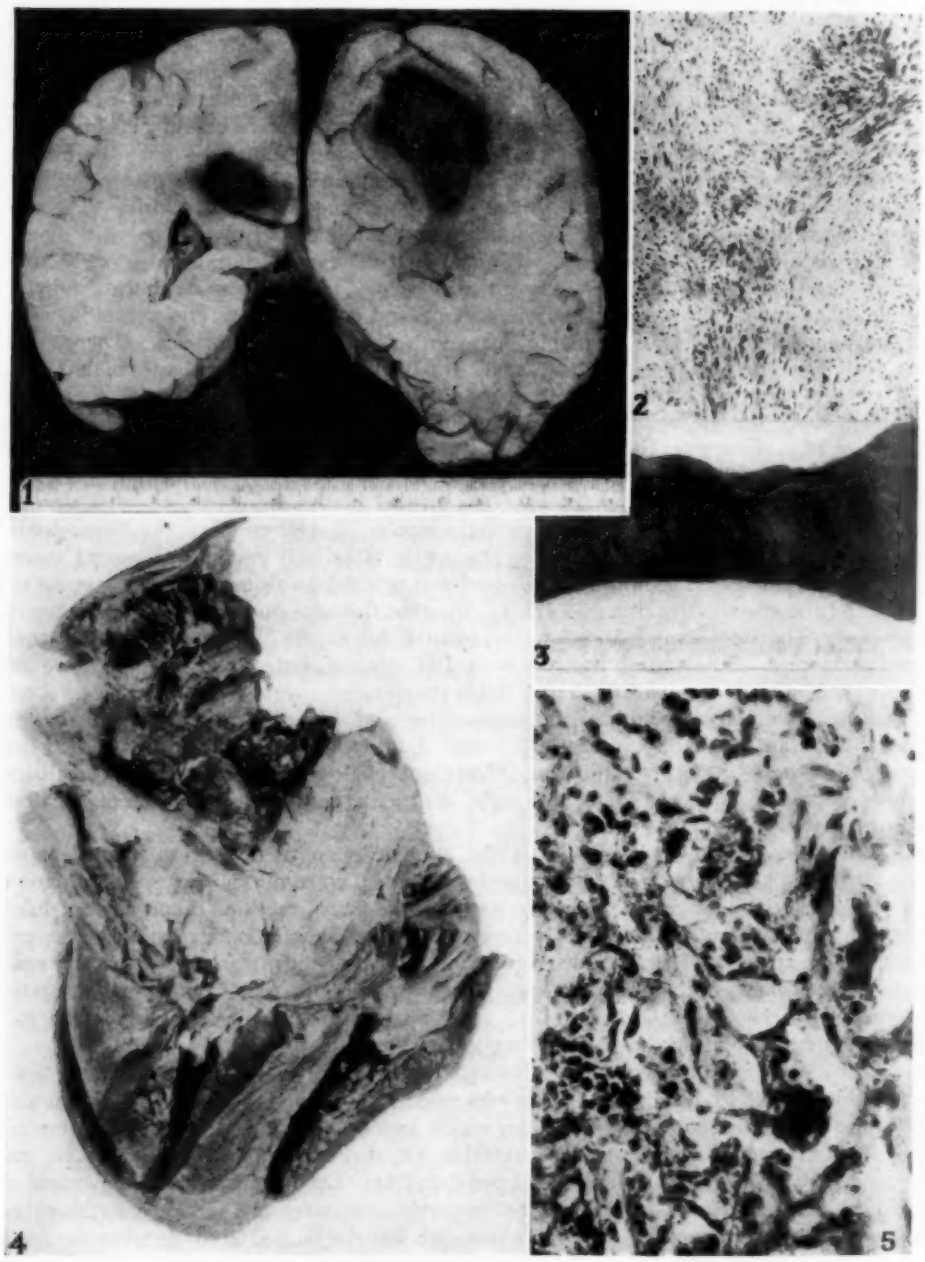

PLATE 1.

FIG. 1. Hemorrhagic tumor masses in brain.
FIG. 2. Photomicrograph of spindle-shaped tumor cells. H & E stain; × 150.
FIG. 3. Hemorrhagic mass in wall of jejunum.
FIG. 4. Thrombus in left auricle.
FIG. 5. Photomicrograph of blood sinuses in tumor. H & E stain; × 500.

white male. It was 180 cm. in length and weighed 140 pounds. A shallow decubitus ulcer was present on the left hip. The skin contained no nodules, warts, or areas of pigmentation. Two small, firm, round hemorrhagic nodules were present in the greater omentum; these were composed of a central mass of gray-white tissue surrounded by a zone of hemorrhage. A similar mass was found in the wall of the jejunum (figure 3). A healed aortic and mitral valvulitis with stenosis of the mitral valve was present in the heart. The left auricle was almost completely filled with a huge thrombus which extended into the left pulmonary vein (figure 4). No macroscopic tumor foci were discovered in the heart. All lobes of the lungs were studded with variable-sized, firm, round nodules of gray-white tumor tissue; these nodules were surrounded by narrow zones of hemorrhage and had a granulomatous appearance. One hilar lymph node was likewise involved. Similar macroscopic foci of the tumor were present in the wall of the stomach (with ulceration of the mucosa), liver, spleen, kidneys, thoracic and lumbar vertebrae, and brain (figure 1). The lesions were particularly numerous in the cerebrum, where both hemispheres and their motor areas contained multiple nodules. The brain stem and cerebellum were not involved. Two guinea pigs were inoculated with fresh tumor tissue. One was sacrificed at 79 days and was found free of lesions. The second animal was alive at 131 days without evidence of disease.

Microscopically the tumor masses varied in appearance. The overall picture was that of a granulomatous hemorrhagic sarcoma with a pleomorphic spindle cell as the dominant structural unit (figure 2). In the vertebral bone marrow the spindle cells were more differentiated than elsewhere and had a whorled arrangement. Formation of blood channels and sinusoids was particularly prominent (figure 5). In some places the blood channel walls appeared to be formed by the spindle cells whereas in other areas they were lined by endothelium. Extensive areas of hemorrhage were present in all lesions. The combination of the spindle cells with the numerous blood channels created a granulomatous appearance in many fields. Areas of necrosis with polymorphonuclear leukocytic infiltration were common. There were two accumulations of atypical cells with round or oval hyperchromatic nuclei in the left auricular thrombus. The thyroid contained a small zone occupied by pleomorphic tumor cells.

Summary

A case of Kaposi's disease (disseminated visceral idiopathic hemorrhagic sarcoma) has been presented including the clinical picture as well as the necropsy findings. This case is of particular interest because of involvement of the thyroid gland and of the brain; to our knowledge there is no recorded instance of involvement of these structures. Disseminated visceral lesions as presented by this case, in the absence of dermal manifestations, are extremely unusual.

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SYPHILITIC HEART DISEASE PROBABLY DUE TO CONGENITAL SYPHILIS; REPORT OF TWO CASES*

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IT is very difficult to establish the diagnosis of syphilitic aortitis in children and adolescents, and confirmation by pathological study is absolute only if the *Treponema pallidum* is found in the aorta. Stolkind [1] emphasized that the *Treponema pallidum* is not found in the aorta of children with congenital syphilis who are more than one year old, and for this reason the diagnosis of congenital syphilitic aortitis has rarely been proved in older children or adolescents. McDonald [2] has indicated that the aortic lesions of congenital syphilis differ in no way from those of the acquired form.

The order of frequency with which McCord [3] found the spirochete in various organs in 243 fetal autopsies is as follows: lungs, kidneys, liver, spleen, adrenals, thymus, heart, spinal cord, and aorta. At times all the organs mentioned harbored the organism, at times only one or two organs. However, he felt that if the *Treponema pallidum* were found in one organ it could be found in all.

Yampolsky and Powel [4] were of the opinion that aortic lesions heal rapidly when antisyphilitic therapy is instituted early in life, and that the stigmata of early syphilitic infection are rarely seen in later life.

Cole [5] has reported that the average duration of life in vigorously treated cases of established syphilitic aortitis in adults is 85 months, whereas in the untreated group it is 34 months. Antisyphilitic therapy has, therefore, an allaying effect on the aortic and other lesions of acquired syphilis, but does not entirely heal the aortic lesions existing before the onset of treatment.

Morhardt [6] has discussed several interesting aspects of the pathogenesis of syphilitic aortitis. He has written that superinfection rarely occurs in syphilis but that the tertiary stage of acquired syphilis is the period in which it is most likely to occur, that is, 15 to 20 years after the primary infection. Therefore, it would seem reasonable that a congenital syphilitic after the age of puberty may be susceptible to the *Treponema pallidum* and that superinfection may be responsible for any discoverable syphilitic lesions. Also, a state of syphilitic allergy may exist in the descendants of infected parents, and this syphilitic allergy may be responsible for an accelerated type of infection, may shorten the period elapsing before the appearance of aortic lesions, and may cause a rapid and progressive aggravation of already existing aortic lesions.

Eleven cases of syphilitic aortitis occurring at autopsy in patients under the age of 30 years were reported by McDonald.[2] There was clinical evidence of aortic valvular disease in two of them. Evidence of congenital syphilis was definitely present in two cases, in neither of which was there aortic valvular disease. There was some degree of narrowing of the coronary ostia in all.

Yampolsky and Powel [4] have described a case which seems to fulfill the requirements for a diagnosis of syphilitic aortitis of congenital origin, a nine year old colored girl whose cord blood and whose mother's blood gave positive

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Wassermann reactions. There were no signs of lesions of the external genitalia to indicate acquired syphilis. At necropsy syphilitic aortitis, great widening of the commissures between the aortic cusps, and extremely narrowed coronary artery ostia were found.

Norris [7] reported two cases of sudden death due to probable congenital syphilitic aortitis. The first was a nine year old girl with a positive Wassermann reaction whose family history indicated that her mother had had two stillbirths, and seven children who had died in early infancy. The father had a right hemiplegia. At autopsy the heart weighed 250 grams, the aortic cusps were separated, and the sinuses of Valsalva and the ascending aorta showed a thickened wrinkled intima. The ascending aorta was dilated and the orifices of both coronary arteries were narrowed but not occluded. Microscopic examination showed irregular intimal thickening, perivascular round cell infiltration in the media with elastic and muscle fibers broken at these points. The adventitia was thick and scarred with scattered perivascular round cell formation. Levaditi stain failed to demonstrate spirochetes in the aorta, myocardium, lungs, spleen, liver or kidney. The second case was a 17 year old male who collapsed while pulling a cartload of wood and died a few minutes later. Necropsy showed left ventricular enlargement, a heart weight of 340 grams, and thickened aortic cusps with rolled margins and thickened points of attachment. The orifice of the right coronary artery was completely occluded by scar tissue extending out of the sinus of Valsalva. The left coronary artery was patent but narrowed by a similar process. Microscopic examination of the root of the aorta and sinuses of Valsalva showed a thickened intima with areas of mononuclear infiltration, areas of rarefaction, and round cell infiltration in the media. The adventitia was thickened with numerous areas of perivascular round cell formation. The aortic valves were fibrous and round cell infiltration was seen where the free edge fused with the aorta. Levaditi stain of the aorta showed no spirochetes.

Norris admitted that there was no conclusive evidence that the disease in either case was due to congenital syphilis. No maternal Wassermann reactions were done, although the stillbirths in the first case suggested syphilis in the mother. Neither patient had other lesions of congenital syphilis, and the Wassermann reactions were not obtained at an early age. He also mentioned the possibility that the infection may have been acquired extragenitally after birth. The age of these two patients does not preclude the possibility that the syphilitic aortitis was acquired, for although the highest incidence of clinical manifestations referable to the aorta occurs 15 to 20 years after the primary infection the interval may range from several months to 50 years.

Nieman and Marks [8] presented the case of an 11 year old girl with productive aortitis and multiple thoracic aneurysms. Pathologic examination revealed the syphilitic nature of the disease. The aorta showed degeneration of the media with secondary fibrosis, fibrotic intimal thickening, proliferation of the vasa vasorum with surrounding inflammatory infiltration, and diffuse sclerosing inflammation of the adventitia. These authors mentioned the possible rheumatic etiology of the aneurysms but were of the opinion that it could be excluded.

To our knowledge the following patients represent the first published case reports of congenital syphilitic aortitis with valvulitis and congestive heart failure occurring in siblings. The record of Case 2, a sister two years older than Case

1, came to our attention during our investigation of Case 1. She was not personally observed by us.

Case Reports

Case 1. S. C., a Negro girl, was seen at the age of five and one-half years at Children's Hospital, Washington, D. C., because of acute pyelitis.

The heart was recorded as normal. The liver and spleen were palpable. The blood Wassermann reaction on two occasions during this hospital stay was strongly positive. Spinal fluid examination, including the Wassermann test, was negative. Antisyphilitic therapy was instituted, and table 1 is a summary of the specific treatment carried out.

Table I

Time Interval	Antisyphilitic Treatment	Blood Test	Weight	Comment
March 1924 to January 1925	17 injections of 0.285 gm. of neoarsphenamine	Wassermann 4 plus	42 to 48 pounds	
1925	27 injections of 0.285 gm. of neoarsphenamine			Ophthalmologist wrote, "Luetic disease with hemorrhage into right eye."
1926	28 injections of 0.3 to 0.36 gm. of neoarsphenamine			
1927	17 injections of 0.3 to 0.36 gm. of neoarsphenamine 14 injections of bismarsen, ½ ampule	April 1927 Wass. 3 plus Kahn 4 plus Nov. 1927 Wass. negative Jan. 1928 Wass. negative		

She was admitted to Gallinger Municipal Hospital for the first time in December 1938. The hospital chart for this admission has been lost. However, the discharge diagnosis was syphilitic heart disease, acute salpingitis, and blindness.

She was readmitted to the Gynecological Department of Gallinger Hospital in October 1939 because of bilateral salpingo-oophoritis. On this occasion the notation was made that she had been blind since the age of 11. She had given birth to a normal child in 1936. The significant findings other than those related to her pelvic difficulties were as follows: Blood pressure 125 mm. Hg systolic and 50 mm. diastolic, bilateral keratitis, heart enlarged downward and to the left with the maximal apex impulse in the sixth interspace 10 cm. from the midsternal line. A loud systolic murmur was heard at the cardiac apex and in the aortic area to the right of the sternum. There was a loud diastolic murmur along the left sternal border. Scoliosis of the lower thoracic and upper lumbar vertebrae was described also. The Kahn reaction of the blood was negative.

In October 1940 she was admitted to the Medical Service for evaluation of her cardiac status. This was the first time she was seen by us. Physical examination showed marked systolic pulsation of the arteries of the neck and extremities, and nodding of the head with each contraction of the heart. There was frontal bossing and prominence of the ends of all the long bones. The corneae of both eyes were opaque. Her nose was flattened with a moderate amount of saddling. There were supernumerary cusps of the molar teeth. The cardiac apex impulse was diffuse, with

the point of maximal intensity in the sixth interspace 10.5 cm. from the midsternal line. A loud blowing diastolic murmur was heard along the left sternal border and in the aortic area to the right of the sternum, accompanied by an intense thrill. At the apex a long low-pitched diastolic rumble ending in a slight crescendo was heard. The first sound at the apex was not unusually loud or snapping. The breath sounds were normal. A teleroentgenogram showed a large heart with particular prominence of the left ventricle and what was either an aneurysm or marked dilatation of the ascending aorta (figure 1). Fluoroscopic examination showed a much widened and vigorously pulsating ascending aorta without aneurysm. The arch and descending thoracic aorta seemed normal. Kahn reactions of the blood and spinal fluid were negative.

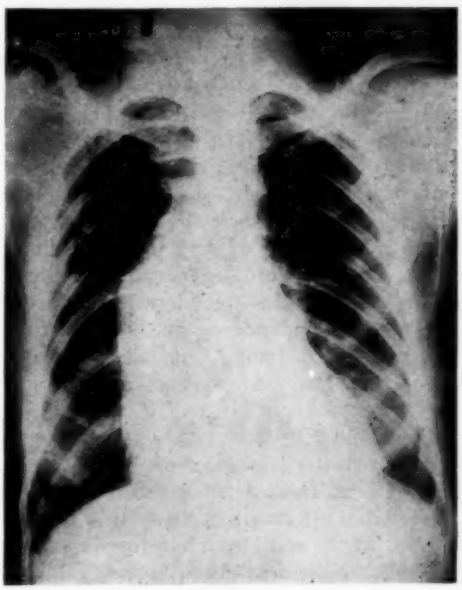

FIG. 1. Teleroentgenogram of Case 1, showing a large heart, with particular prominence of the left ventricle and marked dilatation of the ascending aorta.

In the period from October 1940 to August 1941 there were five admissions to the hospital because of increasing shortness of breath on exertion, leading to considerable dyspnea at rest, and progressively severe substernal pain, radiating down the left arm, related at first to effort and later occurring at rest. Physical examination did not reveal any new findings. The blood pressure was consistently 120 to 130 mm. Hg systolic, and 30 to 40 diastolic in both arms. She was digitalized in October 1940.

On August 10, 1941 she entered the hospital because of nausea and vomiting, dyspnea, and substernal pain on slight effort. The nausea and vomiting were decreased when digitalis was omitted temporarily. On the eighth hospital day she suddenly became very dyspneic and cyanotic. There were frequent premature beats and numerous râles at the bases of both lungs. She died four hours after the onset of the acute distress. Her age at death was 22 years.

Postmortem examination showed a well developed young colored woman of slight body build, with whitish opaque corneae. The pericardial cavity contained

250 c.c. of serosanguinous fluid. The heart was very large, weighing 900 grams. The left ventricle was dilated and its walls especially hypertrophied. Its greatest thickness measured 18 mm. The right ventricle was 5 mm. thick. There was a moderate amount of dilatation of the mitral ring, but all valves except for the aortic were normal. There was marked dilatation of the ascending aorta and aortic ring. The commissures were but slightly widened. The aortic cusps in their central part were moderately rolled and thickened. The orifice of the right coronary artery was slightly narrowed and that of the left coronary artery was decreased by at least 50 per cent owing to thickening of the intima. The wall of the aorta was greatly thickened throughout, measuring 3 mm. There was no tree barking or characteristic syphilitic scarring. The remainder of the gross examination was negative except for a mild degree of passive hyperemia of the lungs and liver.

The heart was sent to Dr. Benjamin Castleman of the Department of Pathology of the Massachusetts General Hospital. He wrote as follows: "Grossly, I was unable to make any diagnosis except marked dilatation of the ascending aorta. The intima seemed to me to be very smooth, and not to show any tree barking or scars. It is true, however, that the aortic cusps were rolled and thickened, and in one place there was slight separation of the cusps at the commissure.

"I took a section through this commissure, as well as a few other sections of the ascending aorta. In our ordinary hematoxylin-eosin stain, there is no doubt of a slight but definite lymphocytic and plasma cell infiltration around the vasa vasorum of the adventitia. I could not be sure of any in the media. Elastic tissue stains, however, of the media show a very severe degeneration of the elastica (figure 2). In the usual case of syphilitic aortitis, this degeneration is ordinarily accompanied by cellular infiltration. There is no evidence of that here. However, it is conceivable that the process is so old, namely congenital, that all evidence is now gone. I would have to agree, therefore, that the best diagnosis is syphilitic aortitis, probably congenital."

Case 2. B. C., a 12 year old Negro female, was admitted to Gallinger Municipal Hospital on March 28, 1929 with the complaint of dyspnea. She died April 9, 1929. It was learned that she had been treated at Children's Hospital, and review of her record there gave the following information. She was a full term baby. She was said to have been "purple" at birth, and bled from the nose for four days. When she was two and one-half weeks old she was admitted to Children's Hospital because of chafing of her buttocks. Examination showed peeling of the soles and palms, and excoriation of both buttocks. The liver and spleen were readily felt. The weight of the child was 7¼ pounds. The diagnosis was congenital syphilis. There is no record of a blood Wassermann at that time. Seven years later she was seen in the Out-Patient Department of Children's Hospital. The blood Wassermann was strongly positive. Antisyphilitic therapy was begun on June 14, 1924. A summary of the treatment is shown in table 2.

She was admitted to the ward of Children's Hospital on August 23, 1924 because she was not doing well. There was some disagreement concerning the exact nature of a heart murmur (or murmurs) although all examiners agreed there was a loud important murmur (or murmurs) present. Roentgen-ray of the chest on August 25, 1924 showed "hypertrophy of the left side of the heart."

Physical examination on admission to Gallinger Municipal Hospital in March 1928 revealed a markedly dyspneic and cyanotic Negro girl. Both corneae were scarred and opaque. Her extremities were cold and her body was covered with profuse perspiration. There were marked systolic pulsations of the carotid vessels. The upper incisors were peg-shaped but not notched. The cervical veins were distended and there were distinct pulsations in the suprasternal notch with a questionable pulsating tumor mass in this location. There was noted a marked precordial bulge and

FIG. 2. Histological section from aorta of Case 1 magnified approximately 600 times. Verhoeff's elastic tissue stain. The marked destruction of elastic tissue is shown by the large number of irregular pale areas.

diffuse cardiac impulse. The apical impulse was most intense at the left anterior axillary line. A systolic murmur was heard at the cardiac apex, transmitted to the left and also heard posteriorly. A presystolic apical murmur was also heard by

TABLE II

Time Interval	Antisyphilitic Treatment	Blood Test	Weight	Comment
June to December 1924	1 i.v. injection 0.125 gm. and 15 i.v. injections of 0.33 gm. neoarsphenamine	Wassermann 4 plus		
1925	23 injections of .33 gm. neoarsphenamine	June 1925 Wass. 4 plus Oct. 1925 Wass. 1 plus	48 pounds	
1928	31 injections of .34 gm. neoarsphenamine	Nov. 1926 Wass. negative		
July 1927 to January 1928	15 injections of ¼ ampule bismarsen	Jan. 1928 Wass. negative June 1928 Wass. negative		Discharged from Antiluetic Clinic March 16, 1928

some examiners. In the aortic area along the right sternal border a diastolic murmur was heard. The pulmonary second sound was accentuated. There was dullness at both lung bases with moist râles in the same area. The abdomen was distended and tympanitic with the liver edge one to two fingers' breadth below the costal margin. There was no edema noted. The temperature was 94.6° F., pulse 100, respirations 60, blood pressure 140 mm. Hg systolic and 90 mm. diastolic. The red cell count was 3,900,000 with 62 per cent hemoglobin; the white cell count was 20,000 with 80 per cent polymorphonuclears, 2 per cent young forms, and 18 per cent lymphocytes. The specific gravity of the urine was 1.022, and there was a large amount of albumin present as well as numerous hyaline casts. The non-protein nitrogen was 64.2 mg., creatinine 1.7 mg. The blood Kahn reaction was negative.

She was digitalized and given sedatives and glucose intravenously. Her condition improved during the following six days except for the development of pitting edema of the lower extremities and signs of digitalis intoxication. Electrocardiogram on April 3, 1929 showed sinus tachycardia, rate 115, P–R interval 0.2 second, upright T-waves in Leads I and II, diphasic T-waves in Lead III, and slight sagging of the S–T segments in Leads II and III.

After the first week in the hospital, she grew steadily worse. There was increasing dyspnea and cyanosis. The temperature was usually subnormal, but occasionally it rose to 100.5° F. She died on the twenty-first hospital day.

Postmortem examination showed marked enlargement of the heart, particularly to the left. The pericardium was normal. When the heart was opened, all chambers were found to be dilated, particularly those of the left ventricle and left auricle. The wall of the left ventricle was markedly thickened, measuring 17 mm. There was marked sagging of the commissures of the aortic valve and the leaflets were curled. The aorta was moderately dilated above the valves and there were diffuse linear striations through the thoracic aorta. There was a small amount of free fluid in each pleural cavity. Both lungs were moderately congested and edematous. The left lung was slightly compressed by the enlarged heart. The liver was found to extend three fingers' breadth below the costal margin. On section it was found to be firm and smooth. The brain was described as appearing normal on cut section. The pathological diagnosis was syphilitic heart disease. Unfortunately, histologic sections from this case are not available, nor is there an adequate description of them.

Discussion

Wassermann or Kahn tests of the mother's blood or of the umbilical cord blood were not made in either of these cases, and it is possible that extragenital syphilis may have been acquired in either or both between the time of birth and the discovery of their positive reactions. However, the diagnosis of congenital syphilis in the first patient seems to be reasonably certain on the basis of the positive Wassermann reaction at the age of five years and the development of interstitial keratitis even though she was receiving antisyphilitic treatment. It does not seem possible to explain the clinical picture noted first three years before her death, of angina pectoris, dilatation of the ascending aorta, free aortic regurgitation (the rumbling diastolic murmur at the cardiac apex undoubtedly represented an Austin Flint murmur), and the pathologic findings by any other process than syphilitic aortitis. The occurrence of late cardiovascular syphilis despite reasonably good (though inadequate by present day standards) antisyphilitic treatment is unusual, but possible. The Coöperative Clinic Group has reported [10] that despite adequate syphilitic treatment about 10 per cent of patients who were at least two years of age at the start of treatment showed relapse or progression of the disease.

The other patient reported here presents a similar picture and most of the above statements apply to this case also. The skin and mucous membrane changes frequently seen in congenital syphilis were observed when she was two and one-half weeks of age, although the blood Wassermann reaction was not recorded until seven years later. The appearance of interstitial keratitis is further evidence of congenital syphilis. In this patient antisyphilitic treatment was scattered over a period of three and one-half years, and the difference in the treatment of the two patients may account, at least in part, for the earlier development of syphilitic aortitis and its more rapid course in the second patient.

Although the *Treponema pallidum* was not demonstrated in either case at postmortem examination and good sections for histological study were not available from the second case, the pathological findings seem sufficiently characteristic to warrant a diagnosis of syphilitic heart disease. It does not seem possible to explain the histologic findings from the sections of the aorta of the first patient otherwise than on the basis of syphilis.

Summary

The occurrence, despite specific treatment, of syphilitic heart disease in sisters aged 22 and 12 years at the time of death is reported. It is probable that the heart disease in both patients was due to congenital syphilis.

We are grateful to Dr. Harold V. Connerty, pathologist at Gallinger Hospital, for his help.

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EDITORIAL

ETIOLOGY AND TREATMENT OF CIRRHOSIS

Up until the last decade portal cirrhosis of the liver was generally regarded as a hopeless disease which must sooner or later terminate fatally in spite of all therapeutic efforts. While granting that the etiology of the disorder was poorly understood, many were content, on the basis of purely circumstantial evidence, to point an incriminating finger at alcohol as the chief offender. Although there can be no question that alcoholism is the most common antecedent factor in victims of cirrhosis in this country, Patek [1] found that in 30 per cent of cirrhotic patients seen at autopsy no history of alcoholism was obtained. He suggested that the etiologic rôle of alcoholism is an indirect rather than a direct one and that alcohol per se does not cause cirrhosis of the liver. The fact that the disease occurs commonly in India, Java, and Ceylon, where alcoholism is rare, would support such an interpretation. Moreover, cirrhosis is known to follow severe toxic hepatitis, as for example from carbon tetrachloride or certain arsenical drugs, and so-called infective or epidemic hepatitis in non-alcoholic individuals. Since alcoholic beri-beri and pellagra have been shown to be similar to the endemic forms of these diseases, it seemed plausible to Patek that the correlation between alcoholism and cirrhosis might likewise be due to a coexisting nutritional deficiency. The heavy drinker will frequently subsist on alcohol alone for long periods with little or no food; thus it would seem reasonable to assume that many of the morbid states to which the alcoholic is peculiarly subject are primarily manifestations of nutritional deficiency. Alcohol may conceivably exert toxic effects in the face of a poor diet, but it must play a minor rôle at best, since all of the deficiency syndromes may develop in total abstainers on deficient diets.

In the experimental field an abundance of evidence has accumulated over the past twenty years attesting to the etiologic rôle of nutritional deficiency in the production of liver disease. Allan [2] and his associates in 1924 reported that depancreatized dogs receiving adequate amounts of insulin and a diet of lean meat, sucrose, and bone ash did not survive for longer than a few months. They further observed that failure of liver function due to fatty infiltration of the liver found in such animals could be prevented by adding raw pancreas to the diet. These observations deserve special recognition in that they provided the essential stimulus to extensive research in

[1] (a) Patek, A. J., and Post, J.: Treatment of cirrhosis of the liver by nutritious supplements rich in vitamin B complex, Jr. Clin. Invest., 1941, xx, 481. (b) Patek, A. J.: Dietary treatment of Laennec's cirrhosis with special reference to early stages of the disease, Bull. New York Acad. Med., 1943, xix, 498.

[2] Allan, F. N., Bowie, D. J., MacLeod, J. J. R., and Robinson, W. L.: Behavior of depancreatized dogs kept alive with insulin, Brit. Jr. Exper. Path., 1924, v, 75.

widely scattered laboratories on lipotropic substances, or substances preventing the deposition of fat in the liver, among them lecithin, "lipocaic," choline, methionine, and inositol. This experimental work may be briefly summarized as follows: Fatty livers and eventually cirrhosis have been produced in normal dogs, rats, and rabbits, maintained on diets high in fat and low in protein or certain highly purified diets. These liver changes may be prevented by increasing the intake of protein (particularly casein), by the addition of yeast or such lipotropic substances as have been enumerated. Although certain discrepancies crop up in the reported results, depending upon the composition of the diet and the type of experimental animal used, yet the evidence is most convincing that crude sources of vitamin B complex and such relatively simple chemical substances as choline and methionine exert a remarkable protective action upon the liver. It has further been found that the addition of cystine to certain of the diets may aggravate the hepatic lesions. The whole problem of cystine-methionine-choline offers a fascinating field for future research.

Undoubtedly, clinical and experimental observations have been equally important in giving impetus to the development of the current treatment of human cirrhosis by a nutritious diet high in calories, protein, and vitamins. Early in this century diets low in all constituents were usually prescribed for cirrhotic patients in order to "spare" the diseased liver as far as possible. In the 1920's, as a result of animal experiments showing the value of a high carbohydrate intake in protecting the liver against certain poisons, diets high in carbohydrate (but still relatively low in protein) were introduced into the therapy of cirrhosis in human beings. Saline purges and diuretics were freely employed, while surgical procedures were devised to improve collateral circulation in the hope of relieving ascites. It was not until 1937 that Patek first reported promising results from the treatment of cirrhosis with a high-caloric diet, rich in protein as well as carbohydrate and fat, and supplemented with large amounts of brewer's yeast powder, vitamins, and injections of liver extract. This contribution marks the beginning of a new era in the therapy of cirrhosis. Convinced that the improvement that followed treatment was beyond chance expectations, Patek was encouraged to extend his therapeutic project to embrace a larger series of patients over a longer period of time. By comparing the results of such treatment in 54 patients suffering from decompensated cirrhosis with a control series of 386 "untreated" patients, he was able to present statistically supported evidence of the efficacy of his therapeutic regimen. Of the treated group 60 per cent experienced spontaneous disappearance of ascites in contrast to only 7 per cent of the control group. The survival rate for patients two years after the onset of ascites was 45 per cent for the treated group as against 22 per cent for the "untreated." Patek predicts with good reason that far superior results might be expected if the dietary treatment could be instituted earlier in the disease before signs of hepatic decompensation had appeared.

Fleming and Snell [3] have obtained similar results in the treatment of 50 cirrhotic patients with a diet that differed materially from Patek's diet in that it was higher in carbohydrate, low in fat, and high in protein not derived from meat sources, whereas Patek gave large servings of meat and as much as 175 grams of fat daily. The basis for this change in protein composition was Bollman's observation that animals with hepatic injury are made worse by administration of meat or meat extracts while tolerating protein from other sources without harmful effect. Snell also supplemented his diet with various pure vitamins, crude oral liver extract, and yeast or yeast concentrates. Subsequently, Keefer and Fries [4] have stressed the therapeutic value of a high carbohydrate, low fat diet with a moderate protein content, supplemented with vitamin preparations and liver extract, in a series of 70 alcoholic patients with fatty livers. They regard the fatty liver as the precursor of cirrhosis, but point out that jaundice, ascites, and death may occur during the stage when the liver is filled with fat and before actual fibrosis has developed. The recognition of the disorder in its early stages and the use of appropriate treatment was followed in many cases by recovery.

In view of the volume of experimental work on the lipotropic action of choline, it was only natural that this substance should be given a cautious therapeutic trial in the treatment of cirrhosis and fatty liver in man. Russakoff and Blumberg [5] have only recently reported highly suggestive evidence that choline exerts a beneficial effect on the clinical course of patients with decompensated cirrhosis. Their patients were placed upon a low-fat Patek dietary regimen supplemented with 1.5 to 6.0 grams of choline chloride daily. No untoward effects from the choline were noted if it was administered orally after meals. Seven of the nine patients treated adequately with choline improved, and it was the opinion of the authors that in several instances the improvement was more rapid than might have been expected from the dietary regimen alone. In a current article [6] reviewing the various aspects of the modern treatment of cirrhosis the writer reports suggestive beneficial effects from the addition of choline to the Patek regimen in several cases so treated. It is as yet too early to draw definite conclusions as to the value of choline in the therapy of human cirrhosis, but certainly further trial of choline, and possibly of methionine also, is desirable in patients with cirrhosis, fatty liver, and acute hepatitis, no matter what the etiology may be.

These recent clinical observations on the dietary treatment of cirrhosis may then be briefly summarized in the following manner: The most promis-

[3] Fleming, R. G., and Snell, A. M.: Portal cirrhosis with ascites: an analysis of 200 cases with special reference to prognosis and treatment, Am. Jr. Digest. Dis., 1942, ix, 115.

[4] Keefer, C. S., and Fries, E. D.: The fatty liver—its diagnosis and clinical course, Trans. Assoc. Am. Phys., 1942, lvii, 283.

[5] Russakoff, A. H., and Blumberg, H.: Choline as an adjuvant to the dietary therapy of cirrhosis of the liver, Ann. Int. Med., 1944, xxi, 848.

[6] Barker, W. H.: The modern treatment of cirrhosis of the liver, Med. Clin. N. Am., March, 1945.

ing treatment of fatty liver and cirrhosis today would appear to consist in the administration of a nutritious diet high in calories, carbohydrate, protein, and vitamins, especially the vitamin B complex, but relatively low in fat. The high protein content is particularly important since it is generally agreed that the hypoproteinemia (or more accurately hypoalbuminemia) so common in patients with liver disease plays a more prominent rôle than portal obstruction in the causation of ascites. The protein should be supplied in the form of lean meat, liver, eggs, milk, and cheese. There is highly suggestive evidence that injections of crude liver extract and the oral administration of choline may prove to be valuable supplements to the dietary regimen. On such a regime almost unbelievable improvement has been observed in patients with severely decompensated cirrhosis. Earlier diagnosis and early institution of an adequate dietary program should not only arrest the progress of the disease but actually result in clinical cures in the vast majority of patients.

In addition to this dietary program, certain adjunctive therapeutic measures must frequently be employed depending upon special problems arising in various patients with cirrhosis. Among these procedures are the intramuscular injection of vitamin K in patients with hemorrhagic diathesis due to hypoprothrombinemia; transfusions in patients with massive hemorrhage; careful regulation of salt and fluid intake to forestall an increase in ascites and edema on the one hand or hypochloremia with dehydration on the other; the use of diuretics and, if these fail, paracentesis for relief of intractable ascites; and the various surgical operations designed to relieve ascites and to prevent hematemesis. Of the latter, omentopexy after a brief period of popularity has been largely discarded as an almost useless procedure with a high mortality rate. Cirrhotic patients tolerate anesthesia poorly and hence are not good operative risks. Injection of varices through the esophagoscope and ligation of the coronary vein of the stomach may serve to reduce the incidence of hematemesis. Splenectomy may be followed by striking improvement in an occasional patient but is too radical a procedure to be justifiable in many instances. Operations designed to shunt blood from the portal system to the vena cava may prove to be the ultimate answer to the problem.

It must be obvious that the final word has not been said as regards an ideal treatment for cirrhosis of the liver. Nonetheless, with the advent of modern dietary therapy and the improvement in surgical technic, the victim of cirrhosis today may rightly feel far more optimistic about his prospects of survival than he could have felt 50 years ago or even 10 years ago.

REVIEWS

The Avitaminoses. By WALTER H. EDDY, Ph.D., and GILBERT DALLDORF, M.D. 438 pages; 23.5 × 15.5 cm. The Williams and Wilkins Company, Baltimore. 1944. Price, $4.50.

The three years which have elapsed between the second and third editions of this volume have been marked by the discovery of many new facts in the vitamin field. The authors found it necessary to revise and reset the entire volume in order to cover these many changes. They have tabulated more of their material and have regrouped related figures and formulae with the result that they have presented up to 50 per cent more material without increasing the length of the book.

The material relating to the chemical nature and function of the vitamins and that concerning the mild and extreme deficiency states have been put in sections one and two of the volume, respectively. The third section includes a new chapter on vitamin assay methods and one on laboratory tests useful in the diagnosis and study of the vitamin deficiency states. The chapters on the chemical nature of the vitamins and on cellular oxidation have been rewritten and the relationship between certain vitamins and oxidation reduction systems has been stressed. In addition to the members of the B complex discussed in the previous edition, inositol, para amino benzoic acid, biotin, choline, and folic acid are included in the chemical characterization of members of the B complex. This brings to 15 the vitamins listed in the volume as proved by chemical means to exist.

The chapter on vitamin requirements is now based primarily upon the recommendations of the Food and Nutrition Board of the National Research Council. The U. S. Food and Drug Standards for label control are also cited.

"The Avitaminoses" should continue to be a valuable reference volume for anyone interested in the vitamin field.

M. A. A.

BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Anatomy as Basis for Medical and Dental Practice. By DONALD MAINLAND, M.B., Ch.B., D.Sc., F.R.S.E., F.R.S.C. 863 pages; 24 × 16.5 cm. 1945. Paul B. Hoeber, Inc., New York. Price, $7.50.

Approved Laboratory Technic. Fourth Edition. By JOHN A. KOLMER, M.S., M.D., Dr.P.H., Sc.D., LL.D., L.H.D., F.A.C.P., and FRED BOERNER, V.M.D. 1017 pages; 25 × 17 cm. 1945. D. Appleton-Century Company, New York. Price, $10.00.

Recent Advances in Endocrinology. Fifth Edition. By A. T. CAMERON, M.A., D.Sc., F.R.I.C., F.R.S.C. 415 pages; 14 × 20 cm. 1945. The Blakiston Company, Philadelphia. Price, $5.00.

The Marihuana Problem in the City of New York. By the Mayor's Committee on Marihuana. 220 pages; 23.5 × 15.5 cm. 1944. The Jaques Cattell Press, Lancaster, Pennsylvania. Price, $2.50.

The Abortion Problem. Proceedings of the Conference Held under the Auspices of the National Committee on Maternal Health, Inc., at the New York Academy of Medicine, June 19 and 20, 1942. HOWARD C. TAYLOR, JR., M.D., Conference

Chairman. 182 pages; 23.5 × 15.5 cm. 1944. The Williams and Wilkins Company, Baltimore.

Essentials of Allergy. By LEO H. CRIEP, M.D., with a foreword by ROBERT A. COOKE, M.D. 381 pages; 20 × 13 cm. 1945. J. B. Lippincott Company, Philadelphia. Price, $5.00.

Casualty Work for Advanced First-Aid Students. By A. W. MACQUARRIE, M.B., Ch.B (Edin.). 231 pages; 12.5 × 9.5 cm. 1944. E. & S. Livingstone Ltd., Edinburgh (Imported by the Peter Reilly Co., Philadelphia). Price, $1.80.

Arterial Injuries. Early Diagnosis and Treatment. By The Vascular Injuries Sub-Committee of the M.R.C. War Wounds Committee. Medical Research Council War Memorandum No. 13. 24 pages; 24.5 × 15 cm. 1944. His Majesty's Stationery Office, London. Price, $.10.

The Treatment of "Wound Shock." (Instructions produced by the Medical Research Council Committees on Traumatic Shock and on Blood Transfusion, in coöperation with the Army Medical Service.) Medical Research Council War Memorandum No. 1—Second Edition. 32 pages; 24.5 × 15 cm. 1944. His Majesty's Stationery Office, London. Price, $.15.

Internal Medicine: Its Theory and Practice in Contributions by American Authors. Fourth Edition. Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P. 1518 pages; 25.5 × 15.5 cm. 1945. Lea & Febiger, Philadelphia. Price, $10.00.

Microbiology and Pathology. Third Edition. By CHARLES F. CARTER, B.S., M.D. 777 pages; 22.5 × 14.5 cm. 1945. C. V. Mosby Company, St. Louis. Price, $3.50.

Physical Demands of Daily Life. An Objective Scale for Rating the Orthopedically Exceptional. By GEORGE G. DEAVER, M.D., and MARY ELEANOR BROWN, M.A. 36 pages; 23 × 15.5 cm. 1945. Institute for the Crippled and Disabled, New York City. Price, $.10.

Chronic Pulmonary Disease in South Wales Coalminers. II. Environmental Studies. A. Report by the Committee on Industrial Pulmonary Disease. B.–G. Reports on Physical, Chemical and Petrological Studies by T. BEDFORD and C. G. WARNER; H. V. A. BRISCOE, P. F. HOLT, N. SPOOR and others; G. NAGELSCHMIDT; A. BRAMMALL and J. G. C. LEECH; D. HICKS and G. NAGELSCHMIDT; J. IVON GRAHAM and D. F. RUNNICLES; and coworkers. (Medical Research Council.) 222 pages; 24 × 15.5 cm. 1943. His Majesty's Stationery Office, London. Price, 10s. 6d. net.

COLLEGE NEWS NOTES

New Life Members

Since the publication of the last issue of the Annals of Internal Medicine, the following Fellows of the College have become Life Members (listed in the order of subscription):

Dr. Harold F. Koppe, Dayton, Ohio
Dr. Harvey M. Ewing, Montclair, N. J.
Dr. Homer Deeter Cassel, Dayton, Ohio
Dr. Otto A. G. Reinhard, Lincoln, Nebr.
Dr. Charles Henry Parsons, Concord, N. H.
Dr. Lawton M. Hartman, York, Pa.
Dr. Leopold Shumacker, Chattanooga, Tenn.
Dr. Anita Mary Mühl, San Diego, Calif.
Dr. Donald R. McKay, Buffalo, N. Y.
Dr. William Lindsay Miller, Gadsden, Ala.
Dr. Samuel G. Shepherd, Philadelphia, Pa.
Dr. William D. Stroud, Philadelphia, Pa.

A.C.P. Members in the Armed Forces

Dr. Aloysius J. B. Connolly (Associate), Washington, D.C., is a Lieutenant Commander in the U. S. Naval Reserve, having been on duty since 1943, but not previously recorded with the College. This brings the total number of members who have entered upon military duty to 1,856.

The following members of the College have been honorably discharged:

Dr. William W. Alexander (Major, MC, AUS), Florence, Ala.
Dr. Chester S. Fresh (Major, MC, AUS), New Orleans, La.

Gifts to the College Library

Book

F. Dennette Adams, F.A.C.P., Colonel, (MC), AUS—"Physical Diagnosis," 13th Edition.

Reprints

J. Edward Berk, F.A.C.P., Captain, (MC), AUS—1 reprint.
Dr. Walter L. Bierring, F.A.C.P., Des Moines, Iowa—1 reprint.
Abraham G. Cohen, (Associate), Major, (MC), AUS—1 reprint.
Dr. Julius H. Comroe, Jr., F.A.C.P., Philadelphia, Pa.—4 reprints.
Dr. C. C. deGravelles, F.A.C.P., New Iberia, La.—1 reprint.
Dr. M. V. Hargett, F.A.C.P., Hamilton, Mont.—1 reprint.
Dr. Jerome G. Kaufman, F.A.C.P., Newark, N.J.—1 reprint.
William C. Meredith, F.A.C.P., Lieutenant Commander, (MC), USNR—1 reprint.
Julius R. Pearson, F.A.C.P., Captain, (MC), AUS—1 reprint.
Dr. Franklin B. Peck, F.A.C.P., Indianapolis, Ind.—1 reprint.
Dr. Lawrence E. Putnam, (Associate), Washington, D.C.—2 reprints.
Dr. George X. Schwemlein, (Associate), Chicago, Ill.—1 reprint.

Dr. Sidney A. Slater, F.A.C.P., Worthington, Minn.—2 reprints.
Dr. Norman Strauss, F.A.C.P., New York, N.Y.—1 reprint.

Examinations by Certifying Boards

American Board of Internal Medicine, William A. Werrell, M.D., Assistant Secretary-Treasurer, 1301 University Avenue, Madison 5, Wis.

Written Examination: Tentatively scheduled for mid-autumn, 1945, in various centers throughout the United States; also available to candidates in military and naval services at certain of their stations, with permission of their commanding officers. Applications for civilian candidates should be filed by early August. Every effort will be made to accommodate candidates in the Service, regardless of the closing date for the acceptance of applications.

Oral Examination: Oral examinations are tentatively planned for June 6, 7 and 8 in Philadelphia. Consult the Assistant Secretary-Treasurer concerning other oral examinations.

American Board of Dermatology and Syphilology, George M. Lewis, M.D., Secretary-Treasurer, 66 East 66th Street, New York 21, N. Y.

Written Examination: For B candidates, given in different cities throughout the country, April 23.

Oral Examination: For A and B candidates, New York City, June 8–9, 1945.

American Board of Pediatrics, C. A. Aldrich, M.D., Secretary, 115½ First Avenue, S.W., Rochester, Minn.

Written Examination: Tentatively planned about October, 1945.

Oral Examination: New York City, March 29, 30 and 31; and Chicago, May 12–13, 1945. The lists for these oral examinations are reported to be filled already. It is planned to have the next succeeding oral examination during November or December, 1945. Consult the Secretary.

American Board of Psychiatry and Neurology, Walter Freeman, M.D., Secretary-Treasurer, 1028 Connecticut Avenue, N.W., Washington, D. C.

Written Examination: At various cities throughout the country, March 30, 1945.

Oral Examination: Chicago, May 18–19, 1945.

American Board of Radiology, B. R. Kirklin, M.D., Secretary-Treasurer, Mayo Clinic, Rochester, Minn.

This Board conducts only a general oral examination. Exact date of next examination not yet determined, but it will be held during the late autumn, 1945. Consult the Secretary-Treasurer.

American Board of Pathology, F. W. Hartman, M.D., Secretary-Treasurer, Henry Ford Hospital, Detroit 2, Michigan.

Written Examination: Pathologic anatomy, June 13; clinical pathology, June 14; at Temple University School of Medicine, Philadelphia, Pa.

A.C.P. Members, Los Angeles Region, Addressed by Dr. Stroud

Under the Governorship of Dr. Roy E. Thomas, F.A.C.P., members of the College of the Los Angeles region held a dinner meeting on February 23. Dr. William D. Stroud, Treasurer of the College, Philadelphia, was the guest speaker. He outlined the work and plans of the College, and gave a paper on hypertension and capillary fragility. There were about sixty Fellows and Associates present, and the meeting was acclaimed a success.

Lt. Comdr. William M. Silliphant
Rescued from Bilibid Hospital, Manila

Lt. Comdr. William M. Silliphant, (MC), U. S. Navy, was rescued during February from the Japanese military prison camp at Bilibid Hospital, Manila. Commander Silliphant is an Associate of the College and was reported to us as "missing in action" at the time of the fall of the Philippines. We had been unable to confirm any facts about his whereabouts until March 2, 1945, when we received a letter from him, written at the Bilibid Hospital February 1, 1945, before United States Forces had yet reached Manila. Commander Silliphant, however, knew that General MacArthur's forces were not far away, and he had absolute faith that he and other prisoners would surely be rescued soon, and so he couldn't wait but prepared his letter in advance for release immediately after rescue. He said in part, "You may not have been aware that for the past three years, I had been the unwilling guest of His Imperial Majesty of Nippon, and unfortunately had been unable to communicate with you. At the present time I am still behind the enemy lines, but the situation seems to be improving rapidly for us here. I am writing this letter at this time in order to have it ready for the first mail out after our rescuers arrive, and I hope it shall not be too long delayed."

Commander Silliphant was assigned to the U. S. Naval Hospital, Canacao, Philippine Islands, in November, 1941, as Laboratory Officer and Assistant in Medicine. This hospital was subsequently re-organized as the Bilibid Hospital for military prison camps of the Philippine Islands. Further details about Commander Silliphant may not yet be published, but we hope to have further data available later.

Captain Edward L. Bortz in Iwo Jima

Captain Edward L. Bortz, (MC), USNR, of Philadelphia, for many years active on the College program of postgraduate courses, and the College Governor for Eastern Pennsylvania, served throughout the Iwo Jima campaign on one of the Evacuation Hospital staffs. A letter near the end of the campaign relates that our Marines have been magnificent and that there are many heroes among our Privates First Class. He relates how the Medical Officers as well as all others have been sleeping in foxholes, that living is rugged, that they were frequently bombed during the nights and that it is a bit difficult to sleep in the open with shells whistling overhead. On an island so small it is obvious that no one could be far from the front.

Typical Messages from War Areas

The College Office receives many letters from its members in all parts of the world, and acknowledges them with deep appreciation, because the College wishes to maintain its contacts with its members everywhere.

"In December, 1943, I was reassigned to the 219th General Hospital (Pacific area) and since then have been Chief of the Cardiovascular Section and for the past three months Chief of the Officers and Women's Medical Sections as well. This work has been much more pleasing to me, since it is quite in keeping with the sort of work I did in private practice. You may be interested to know that our Chief is Lt. Col. Conrad Acton, Life Member of the College. The chief desire of everyone who has been out here for a long time is that this war may soon be over and that we may return home. We realize that the end is not yet in sight, however, and we realize the importance of good medical care for our soldiers. This is a beautiful

place from most standpoints. Our facilities are probably as good as the Army can offer anywhere, and we have no physical hardships. The separation from our loved ones is the greatest hardship we have to bear."—Captain, (MC), AUS (F.A.C.P., Detroit, Michigan).

Report Changes of Address!

The Annals of Internal Medicine and the Office of the American College of Physicians experience great difficulty in obtaining address changes for subscribers who are in the Armed Forces, and who themselves overlook recording new assignments with the College Office. A great effort is made to follow each member and subscriber, but it is extremely difficult to obtain new addresses except through the individual himself. Many copies of the Annals of Internal Medicine, as well as other journals, are lost because members, especially those on active military duty, fail to record their correct addresses.

Dr. Nelson G. Russell, F.A.C.P., Receives Honor

The Chancellor's Medal of the University of Buffalo was conferred upon Dr. Nelson G. Russell, F.A.C.P., on the occasion of the 45th annual mid-year convocation of the University on February 22.

The citation started, "Nelson Gorham Russell, scientist, soldier, civic leader, teacher and mentor of two generations of physicians . . ." Dr. Russell is a graduate of the Medical School of the University of Buffalo, and he has given many years of devoted service there as Professor of Medicine (now Emeritus). The local press states that in very large part Dr. Russell deserves credit for advancing the School to the high position that it now has among such institutions in the nation; that he has put his impress upon hundreds of young men whose services dignify it.

During World War I he was designated Consultant in General Medicine for an area in which there were some thirty hospitals, the appointment having been made by General Pershing. Dr. Russell received a citation for "exceptionally meritorious and conspicuous services." He also received the Purple Heart.

Dr. Russell is Chairman of the Buffalo Advisory Board of Health and of the Managing Board of the Meyer Memorial Hospital.

"His career has been one of constantly enlarging service. He is an exemplar of the finest traditions of his profession. The Chancellor's Medal was never more worthily bestowed."

Dr. Sidney A. Slater Honored

Dr. Sidney A. Slater, F.A.C.P., Superintendent of the Southwestern Minnesota Sanatorium, at Worthington, Minnesota, and a recognized authority on tuberculosis and public health, will be honored by his alma mater, the Medical College of Virginia, at a special convocation on April 27, when he will receive the degree of Doctor of Science. At the same time Dr. Slater will receive a previously awarded Phi Beta Kappa key.

Dr. Joseph T. Wearn Appointed Dean Western Reserve University School of Medicine

Dr. Joseph T. Wearn, F.A.C.P., Professor of Medicine at Western Reserve University, has been appointed Dean of the School of Medicine. He succeeds Dr. Torald H. Sollmann, F.A.C.P., who retired last July 1, after nearly 50 years of service with the University. Dr. Wearn will continue as Professor of Medicine at the University, and as Director of the Department of Medicine at Lakeside Hospital. He is widely known as a teacher and for his research in medicine. He has written extensively on the physiology of heart disease; diseases of the blood, including leukemia; and other subjects. He is a Consultant to the Surgeon General of the United States Army, Consultant to Research and Development Branch of the Office of the Quartermaster General of the U. S. Army, Chief of the Division of Physiology, Committee of Medical Research, and Chairman of the Subcommittee on Blood Substitutes, of the Office of Scientific Research and Development.

Dr. Wearn went to Western Reserve and Lakeside Hospital in 1929 from Harvard Medical School, where he was Associate Professor of Medicine and Associate Director of the Thorndike Memorial Laboratory and Visiting Physician at the Boston City Hospital.

Postgraduate Courses Offered by the College

The spring 1945 schedule of Courses has been published in several of the preceding issues of this Journal. The roster included five courses: Cardiology, at Columbia University College of Physicians and Surgeons, under Dr. Robert Levy, F.A.C.P., Director; Mechanics of Disease, at Harvard Medical School, under Dr. George Thorn, F.A.C.P., Director; Clinical Medicine-Hematology, at Ohio State University College of Medicine, under Dr. Charles A. Doan, F.A.C.P., Director; Gastrointestinal Diseases, at the Graduate Hospital, Philadelphia, under Dr. Henry Bockus, F.A.C.P., Director; and, Applications of Psychiatry to the Practice of Internal Medicine, at the University of Wisconsin Medical School, under Dr. Hans Reese, F.A.C.P., Director.

The organization of these refresher courses has become one of the most keenly appreciated activities of the College. The demand for these courses among members of the College is greater than available facilities. During the present wartime it is difficult to find faculties that are available and prepared to give courses on the high plane set by the College. There is an admirable willingness to aid the program everywhere.

Two situations conspired during the winter, delaying the appearance of the Postgraduate Bulletin: (1) The program had to be submitted to the Office of Defense Transportation for approval, which resulted in a very considerable delay, during which time the Bulletin could not be released for printing. Finally, the ODT added its conditional approval, providing the registration in any course shall not exceed 50 men who will be using transportation and housing facilities; (2) Although the Postgraduate Bulletin was rushed to completion and sent to most parts of the country by first-class mail, with allowances being made for distances, there were numerous reports of delay or loss in the mails.

Announcements concerning the courses appeared in several issues of the Annals of Internal Medicine with the result that many members registered in advance of the arrival of the Bulletin. All courses were filled to capacity, and many applicants had to be disappointed. In some courses, such as the one in Cardiology in New York City, the faculty could have handled a much larger number; yet the regulations of the Office of Defense Transportation made this impossible, because of limitation of registration.

The program of courses for the autumn of 1945 is already being organized. Dr. Paul White, of Harvard Medical School, will give a 1-week course in Cardiology, repeating the very popular course given by him during the autumn of 1944. Members are invited to write in to the College Headquarters stating the titles of courses desired; the Committee on Postgraduate Courses will make an effort to extend the program along the lines most desired by the College members.

Dr. R. K. Richards, F.A.C.P., North Chicago, Illinois, addressed the Chicago Neurological Society, January 10, on "The Pharmacology of Tridione, a New Experimental Drug for the Treatment of Convulsive and Related Disorders."

The Society of Medical Jurisprudence conducted a Symposium at the New York Academy of Medicine Building, February 19, on the subject, "Is the Obligation of Providing Medical Care to All—That of the State, the Public or the Medical Profession?" Dr. Nathan B. Van Etten, F.A.C.P., spoke on the subject from "The Standpoint of the Practitioner of Medicine"; Colonel Louis H. Bauer, F.A.C.P., discussed "The Standpoint of Organized Medicine"; Dr. William W. Herrick, F.A.C.P., President of the New York Academy of Medicine, discussed the "Federal Social Security Health Legislation"; Honorable William F. Bleakley, Former Justice of the New York Supreme Court, talked on "The Probable Attitude of the Public in Regard to the Future of Medicine in the United States"; Allen Wardell, Esq., President of the New York City Bar Association, used as his subject, "Should the Medical Profession or the Government Provide Medical Care through Insurance?"; and Mayor Fiorello H. LaGuardia discussed "The Health Insurance Plan of Greater New York."

Since March 15 the WPB has lifted the restrictions on the general distribution of penicillin for civilian use. This release, however, does not apply to the new oral penicillin in tablet form. Many of the manufacturers are developing penicillin for oral use when released by WPB, anticipated in the near future.

Committee on Postwar Medical Service

The Joint Committee on Postwar Medical Service met in Chicago on February 10 and again on March 17. The minutes of the latter meeting are not available when this copy goes to press. Dr. Ernest E. Irons, F.A.C.P., is the Chairman of the Joint Committee. Due to other assignments and duties Dr. Walter W. Palmer, Chairman of the A.C.P. Committee on Postwar Medical Service, recently resigned, and President Irons appointed Dr. George Morris Piersol, F.A.C.P., as Chairman of the Committee, succeeding Dr. Palmer, and Dr. W. W. Herrick, F.A.C.P., New York City, as a member of the A.C.P. Committee.

Among the more important transactions on February 10 was a progress report on the analysis of questionnaires sent to medical officers by Lt. Col. H. C. Lueth, F.A.C.P., liaison officer between the Surgeon General of the Army and the Committee. His report in brief summary was as follows:

1. Future educational desires of medical officers on duty with the Army, Navy, Public Health Service and Veterans Administration were determined by a study of 21,029 returned questionnaires.

2. Nearly 60 per cent of the group, 12,534, wanted to take long courses (six months or longer) of further training in hospital or educational work. About one-

fifth of the group, 4,563, indicated they wished to take short courses (less than six months).

3. There were 3,922 medical officers, or 18.7 per cent of the group, who did not want any future training.

4. Requests for short courses included all specialties. The largest number of requests were for the following specialties in order of frequency: internal medicine, surgery, general review, obstetrics and gynecology, pediatrics, otolaryngology and ophthalmology.

5. The ten most popular special fields of training by means of long courses, in order of frequency of request, were surgery, internal medicine, obstetrics and gynecology, general review, psychiatry and neurology, pediatrics, orthopedic surgery, ophthalmology, radiology and otolaryngology.

6. Nearly two-thirds of the group, 13,333, or 63 per cent, expressed a desire to become certified specialists. There were 3,324 medical officers, nearly 16 per cent of the entire group, already certified by the American specialty boards. The remainder either did not care to be certified or did not mention their desires.

7. Nearly 40 per cent, 8,734 medical officers, came from private practice to the military services. Twenty-two per cent, 4,640, came directly from internships; nearly 10 per cent, 2,191, came directly from residencies, and the remainder came from various types of practice. About 15 per cent failed to answer the question concerning their previous type of medical practice.

8. A comparison of the results of a pilot questionnaire and the present questionnaire was made. Long courses were requested by about one-fifth more men in the final questionnaire than in the pilot questionnaire. Only two thirds as many men requested short courses in the final questionnaire as in the pilot. The difference was attributed to a change in viewpoint of medical officers during the interval between the circulation of the questionnaires rather than to an error in sampling.

Dr. Olin West, Secretary of the American Medical Association, reported that the Bureau of Information is now functioning, and up to that time had completed tabulation of 38 states. He predicted that the Bureau of Information would receive the cordial coöperation of the constituent state medical associations and the component county medical societies. Inquiries coming to the Bureau are more numerous from men who have already been discharged from active service than from those still on duty. The Bureau is collecting information in regard to education, licensure and location. Information on educational facilities will be handled by Dr. Victor Johnson, Secretary of the Council on Medical Education and Hospitals. The question of location in specific communities is a local problem, which will be referred to state agencies. Much confusion in the states has arisen in the selection of hospitals and educational institutions under provisions of the GI Bill; in some states the State Department of Education is advising the Governors—in several states the organization of the work is behind and in others far ahead—and it will be necessary to "tie up" the hospital, educational and licensing elements into a coördinating group. The Committee on Postwar Medical Service will be able to exercise such a coordinating action.

The following resolution was adopted, after discussion in which it was noted that under the GI Bill the Governors of the states are given control over all phases of education for veterans:

> Resolved, That the chair be authorized to appoint a sub-committee to
>
> 1. Draw up recommendations to the Governors of the several states concerning the medical education and postgraduate training of veterans under Title II of Public Law No. 346, the Servicemen's Readjustment Act of 1944, with particular reference to the certification of institutions as qualified to give such training, and

2. Coördinate this effort with related medical and health problems in the state.

Progress Report on Educational Opportunities for Medical Officers. Dr. Victor Johnson presented a progress report on educational opportunities for medical officers, stating that it would be necessary to modify some of the estimates of available residencies on the basis of the analysis presented by Colonel Lueth. He stated that developments so far are promising and, if institutions and individuals involved continue with the same vigor and industry, the need will be met. Further reports will be made to the Committee.

During the discussion of Dr. Johnson's report, the question was asked if all of the residencies that would be available are of a type that would lead to certification by specialty boards, and the reply was that many would be second year training and that those hospitals initiating new residencies would have to be considered by the Council on Medical Education and Hospitals and by the specialty boards. This progress report will be continued at the next meeting.

Minor reports were received from the Subcommittee to Confer with the Surgeons General on Education of Medical Officers and from a Consulting Committee on Army and Navy Plans for Residencies and Graduate Study. The Army was reported to be readjusting the specialties practiced in its general hospitals, and increasing and readjusting the size of the facilities now available. The refresher professional training has been authorized for officers of the Medical Corps who for the past twelve months or longer have been in administrative command. Training will be in hospitals in both medicine and surgery, will be voluntary and available to any officer of the Medical Corps, with priority given to men who have been overseas. Such officers will be ordered to temporary duty to take the course of instruction, at their own request, and will continue in service. It was added that the refresher course plan has nothing to do with the specialties, however, and that the Army has no intention of putting these men into a type of specialized training that would qualify them for specialty board certification.

A representative of the United States Public Health Service reported that in U. S. Public Health Service Hospitals there will be places for about thirty residencies, available after the war. The Public Health Service is conducting a training course in civilian schools for the benefit of U.S.P.H.S. officers, both regular and reserve.

The Subcommittee on Surplus Medical and Hospital Supplies reported that the U. S. Public Health Service had drawn up a plan for the disposal of surplus medical supplies. This Subcommittee was instructed to review the plan and to report back to the Central Committee with recommendations. Dr. George Morris Piersol, F.A.C.P., was appointed a member of this Subcommittee.

There were progress reports from Subcommittees interested in Educational Assistance for Veterans through the Veterans Administration, the Establishment of a Medical Corps in the Veterans Administration, Sources of Funds to be used for Postwar Medical Education, the status of the Army Specialized Training Program and the Navy V-12 Program, and matters of a kindred nature.

News from the Office of the Surgeon General, U. S. Army

Major General Norman T. Kirk, F.A.C.P., The Surgean General, and Brigadier General James S. Simmons, F.A.C.P., Chief of the Preventive Medicine Service, completed a six weeks' tour of the Pacific Theater of Operations during February and March.

Lt. Col. Raymond G. Hussey, F.A.C.P., Director of the Army Industrial Hygiene Laboratory, Baltimore, has retired from active duty to accept an appointment as Dean

of the School of Occupational Health, which he is now organizing at Wayne University, Detroit. Col. Hussey is one of the foremost authorities in the field of occupational health. His development of the Army Industrial Hygiene Laboratory, under the Preventive Medicine Service, represents a new departure in this field of preventive medicine in the U. S. Army. At Wayne University he will organize the first formal program of educational health and medicine.

Col. C. C. Odom, F.A.C.P., is the Commanding Officer of the Mason General Hospital, Long Island, N. Y., where a three months' course in Military Neuropsychiatry is being given, in conjunction with Columbia and New York Universities.

Lt. Col. Burgess L. Gordon, F.A.C.P., of Philadelphia, has been transferred from the Technical Division, Operations Service of the Office of the Surgeon General to the U. S. Army General Hospital, Camp Pickett, Va.

Brigadier General Hugh J. Morgan, F.A.C.P., Consultant in Medicine to the Surgeon General, has been elected a member of the Endowments and Grants Committee of the Army Medical Library. Dr. Arthur H. Sanford, F.A.C.P., of the Mayo Clinic, is also a member of this Committee.

Major Douglass W. Walker (Associate), Executive Officer, Preventive Medicine Service, Office of the Surgeon General, has been promoted to the rank of lieutenant colonel.

Major General George F. Lull, F.A.C.P., Deputy Surgeon General, is President of the Medical Research Board in the Office of the Surgeon General, the purpose of which is to coördinate all medical department research with other staff agencies and components of the Army, as well as with agencies outside the Army. Lt. Col. Leon H. Warren, (Associate), Chief of the Research Coördination Branch, Technical Division, Operations Service, is recorder.

Recent Promotions, Medical Department Officers

Major to Lieutenant Colonel: J. Warren Hundley, Jr., F.A.C.P., Philadelphia, Pa.; Edward G. Thorp, F.A.C.P., Melrose, Mass.; Algot R. Nelson, F.A.C.P., Grand Rapids, Mich.; James E. Cottrell, F.A.C.P., Philadelphia, Pa.; Harold A. Golz, F.A.C.P., Clarksburg, W. Va.; Raymond L. Barrett, F.A.C.P., Longmeadow, Mass.; Hiland L. Flowers, F.A.C.P., Bronx, N. Y.; Douglas M. Gordon, F.A.C.P., Ponca City, Okla.; T. Douglas Kendrick, F.A.C.P., Utica, N. Y.; Charles Stuart Wilson, F.A.C.P., Detroit, Mich.

Dr. Charles E. Leonard, (Associate), who formerly was Assistant in Medicine at the University of Oklahoma School of Medicine, has been appointed Instructor in Psychiatry.

Dr. Dwight O'Hara, F.A.C.P., Acting Dean and Professor of Preventive Medicine, Tufts College Medical School, Boston, was the first speaker on a Graduate Seminar in Industrial Health, Brown University, Providence, February 20, his subject being "Bases of Industrial Medical Practice."

Dr. Paul Brindley, F.A.C.P., Galveston, Dr. May Owen, F.A.C.P., Fort Worth and Dr. John J. Andujar, F.A.C.P., Fort Worth, were elected President, President-elect, and Secretary-Treasurer, respectively, at the Annual Meeting of the Texas Society of Pathologists during January.

The New York Heart Association, which heretofore has been a part of the New York Tuberculosis Health Association, has separated from the latter organization and will continue as an independent society, with headquarters in the building of the New York Academy of Medicine. Dr. Edwin P. Maynard, Jr., F.A.C.P., Brooklyn, is President of the Association; Dr. Harold E. B. Pardee, F.A.C.P., is Chairman of the Finance Committee.

Col. Marion H. Barker, F.A.C.P., of Chicago, recently received the Legion of Merit "for exceptionally meritorious conduct in the performance of outstanding services in the North African Theater of Operations, from January 21, 1944, until July 8, 1944. Assigned to the study of infectious hepatitis, Col. Barker devised a comprehensive and effective plan of investigation and discovered valuable new data concerning its diagnosis, progress, treatment and after-effects. By his keen scientific insight and coördinated labors, he developed methods of treatment and criteria for the disposition of patients suffering from this disease, which prevent undue damage and restore most of those afflicted to their normal activities as healthy individuals, rather than as chronic sufferers. The fighting strength of the Army has been measurably increased by this work. The investigations conducted by Col. Barker are among the outstanding contributions to medical science during this war and are consistent with the highest traditions of research in the Medical Corps of the Army."

Major General George F. Lull, F.A.C.P., Deputy Surgeon General, U. S. Army, gave the principal address, "Some Wartime Problems of the Medical Department and Some of Its Accomplishments," on the occasion of the 75th anniversary of the Raleigh (N. C.) Academy of Medicine, February 2.

"Wartime Medical Research" was the title of the annual Walter L. Niles Memorial Lecture, by Dr. Edwin Cowles Andrus, F.A.C.P., Baltimore, at Cornell University Medical School on February 20.

The name of the Hamilton County (Ohio) Tuberculosis Hospital, Cincinnati, was recently changed by the Board of Trustees to the "Dunham Hospital" in honor of the late Henry Kennon Dunham, F.A.C.P., who served as its Medical Director from 1914 to 1941.

Rear Admiral Edward R. Stitt, F.A.C.P., (MC), U.S.N., Retired, former Surgeon General of the U. S. Navy, was the recipient of a gold medal and an honorarium of $500 for outstanding service in the field of tropical medicine, presented by the American Foundation for Tropical Medicine on February 5.

Col. Harry G. Armstrong, F.A.C.P., (MC), U. S. A., was recently awarded the Legion of Merit for exceptionally meritorious conduct in the performance of services from September 8, 1939, to June 20, 1941.

Major General Shelley U. Marietta, F.A.C.P, (MC), U.S.A., although having reached the statutory retiring age, will be retained as Commanding General of the Walter Reed General Hospital in Washington.

Dr. Charles J. Bartlett, F.A.C.P., Emeritus Professor of Pathology, Yale University School of Medicine, recently celebrated his 80th birthday as guest of honor at a dinner tendered by the New Haven Medical Association.

Dr. J. Arnold Bargen, F.A.C.P., Associate Professor of Medicine University of Minnesota Graduate School, delivered the 24th Annual Beaumont Lecture of the Wayne County Medical Society, Detroit, February 19 on "Modern Concepts of Intestinal Infection."

Dr. Karl D. Figley, F.A.C.P., Toledo, has succeeded Dr. Will Cook Spain, F.A.C.P., New York City, resigned, as Secretary of the American Academy of Allergy. The Academy has built up a fund to constitute an annual Secretary's Prize, and the first recipient of this prize was Dr. J. Harvey Black, F.A.C.P., Dallas, Tex., for his paper, "The Treatment of Urticaria with Synthetic Vitamin K."

The art contest, sponsored by Mead Johnson & Company, "Courage and Devotion Beyond the Call of Duty," has not been cancelled or postponed. The closing date remains May 27, 1946.

There will be no annual exhibit in 1945 of the American Physicians Art Association, however. For full details regarding the $34,000 in prizes, address the Secretary, American Physicians Art Association, Flood Bldg., San Francisco, Calif.

Permanente Foundation Research Fellowships

The Permanente Foundation will offer a limited number of Fellowships for Clinical Research in the fields of medicine, surgery and related specialties. Research Fellowships in the field of internal medicine are announced for investigations in "Cardiac Status in Pneumonia" and "Evaluation of Recent Advances in Peptic Ulcer Therapy."

The Fellowships provide $225 monthly, plus maintenance. For information, address Chairman, Fellowship Committee, Permanente Foundation Hospital, Oakland 11, Calif.

Capt. B. W. Hogan, F.A.C.P., (MC), U.S.N., was recently assigned as Senior Medical Officer on the new hospital ship, U.S.S. *Tranquillity*. The ship is air conditioned throughout and equipped with the finest of medical and surgical facilities. It has 802 permanent beds.

The Society for Investigative Dermatology announces the resumption of publication of their periodical, the *Journal of Investigative Dermatology*, which temporarily suspended publication in 1942 on account of war conditions. The first number of Volume 6 appeared in February. It will be issued bi-monthly, one volume a year, at $6.00 per volume, by The Williams and Wilkins Company, Baltimore 2, Maryland.

Correction

Annals of Internal Medicine, February, 1945, page 327, paragraph 2. ". . . There was an urgent request for the repetition of this course (Cardiology, Boston, Dr. Paul D. White, Director) this coming winter or spring, but Dr. White was so 'busy' (not 'exhausted') that he has asked to have the repetition of the course delayed at least until the autumn of 1945."

War-Time Graduate Medical Meetings

Region No. 3 (New York)—Dr. O. R. Jones, Chairman; Dr. N. Jolliffe, Dr. H. W. Cave.

Induction Center, Grand Central Palace, New York, New York

April 20 Common Wartime Dermatoses—Dr. Frank C. Combes.
April 27 (to be repeated on May 4) Common Allergic Manifestations—Dr. Joseph Harkavy.
May 11 (to be repeated on May 18) Deleterious Effects of Drugs on the Hemopoietic System—Dr. Nathan Rosenthal.
May 25 Deficiency States and Their Recognition—Dr. H. D. Kruse.

Region No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr. B. P. Widmann, Chairman; Dr. J. S. Rodman, Dr. S. P. Reimann.

U. S. Naval Hospital, Philadelphia, Pennsylvania

April 20 Subject to be announced—Dr. George Wilson.
May 4 Subject to be announced—Dr. Frank Adler.
May 18 Health Department Military Liaison in Venereal Disease—Dr. Norman Ingraham.

Region No. 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr. J. A. Lyon, Chairman; Dr. C. R. Edwards, Dr. C. B. Conklin.

Regional Hospital, Camp Lee, Virginia

April 20 Evaluation of the Surgical Risk and Anesthesia—Captain William A. Weiss.
April 27 Prevention and Treatment of Wound Infections with Sulfonamides—Captain James E. T. Hopkins.

Newton D. Baker General Hospital, Martinsburg, West Virginia

April 16 Psychosomatic Medicine—Dr. Claude L. Neale.
Recent Developments in Nutrition—Dr. J. C. Forbes.
May 7 Neuro-Surgical Clinic—Dr. Charles Bagley, Jr.
Chemotherapy in Dysentery—Dr. Lay Martin.
May 21 Narcosynthesis and Hypnoses—Dr. Addison McGuire Duval.
Peripheral Vascular Diseases Due to War-Time Conditions—Dr. J. Ross Veal.

A.A.F. Regional Hospital, Langley Field, Virginia

April 27 Psychosomatic Medicine—Dr. Soloman Katzenelbogen.
Radiology—Dr. Frederick M. Hodges.
May 25—Aviation Medicine—Dr. L. G. Lederer.
Fundamentals of Plastic Surgery—Dr. Robert E. Moran.

Region No. 8 (Western Pennsylvania, Ohio)—Dr. C. A. Doan, Chairman; Dr. P. G. Smith, Dr. F. M. Douglass.

Crile General Hospital, Cleveland, Ohio

April 24 Congenital Anomalies of the Genitourinary Tract—Dr. William E. Lower.

Region No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman; Dr. N. C. Gilbert, Dr. W. H. Cole, Dr. W. D. Gatch, Dr. R. M. Moore, Dr. H. M. Baker, Dr. E. R. Schmidt, Dr. E. L. Sevringhaus, Dr. F. D. Murphy.

Gardiner General Hospital, Chicago, Illinois

April 25 Endocrinology.
May 2 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment.
May 16 Mental Hygiene and the Prevention of Neuroses in War.
May 23 Wound Healing and Tendon Surgery.

Station Hospital, Fort Sheridan, Illinois

April 25 Psychosomatic Medicine.
May 2 Wound Healing and Tendon Surgery.
May 16 Peptic Ulcer, Gall Bladder and Liver Diseases.
May 23 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases.

Mayo General Hospital, Galesburg, Illinois

April 25 Mental Hygiene and the Prevention of Neuroses in War.
May 2 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases.
May 16 Chest Diseases and Diseases of the Larynx.
May 23 Low Back Pain.

Vaughan General Hospital, Hines, Illinois

April 25 Peptic Ulcer, Gall Bladder and Liver Diseases.
May 2 Low Back Pain.
May 16 Heart Disease and Allied Conditions.
May 23 Bone and Joint Infections.

Station Hospital, Camp Ellis, Illinois

April 25 Chest Diseases and Diseases of the Larynx.
May 2 Bone and Joint Infections.
May 16 Arterial Vascular Disease—Traumatic Lesions.
May 23 Repair of Bone in Fractures and Diseases.

Station Hospital, Chanute Field, Illinois

April 25 Conditions Affecting Glucose Metabolism.
May 2 Plexus and Peripheral Nerve Injuries.
May 16 Dermatological Diseases.
May 23 Burns and Plastic Surgery.

Station Hospital, Camp McCoy, Wisconsin

April 25 Heart Disease—Dr. Chester M. Kurtz.
May 2 Repair of Bone in Fractures and Diseases.
May 16 Diseases of the Kidneys—Urogenital Tract.
May 23 Blood Dyscrasias, Malaria, Filariasis.

Station Hospital, Truax Field, Wisconsin

April 25 Diseases of the Kidneys—Urogenital Tract—Dr. Francis D. Murphy.
May 2 Laboratory Diagnosis and Its Relationship to Medical and Surgical Treatment.
May 16 Conditions Affecting Glucose Metabolism.
May 23 Brain and Spinal Cord Injuries.

Billings General Hospital, Indiana

April 25 Diseases of the Intestinal Tract—Medical and Surgical Diagnosis and Care.
May 2 Burns and Plastic Surgery.
May 16 Malignancies in the Army Age Group—Medical X-Ray and Surgical Diagnosis and Treatment.
May 23 Endocrinology.

Wakeman General Hospital, Indiana

April 25 Dermatological Diseases.
May 2 Endocrinology.
May 16 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment.
May 23 Psychosomatic Medicine.

REGION No. 23 (Nevada, Northern California)—Dr. S. R. Mettier, Chairman; Dr. E. H. Falconer, Dr. D. N. Richards.

Station Hospital, Hamilton Field, California

May 2 Early Post-Operative Ambulation of Surgical Patients—Dr. H. Glenn Bell.
May 16 Fractures of the Extremities—Dr. Carl Anderson.
May 30 Diagnosis and Treatment of Arthritis—Dr. Stacy R. Mettier.

Station Hospital, Camp Roberts, California

April 21 Psychosomatic Medicine—Dr. Douglas G. Campbell.
May 19 Diagnosis and Treatment of Arthritis—Dr. Hans Waine.
May 26 The Treatment of Poliomyelitis—Dr. Henry D. Brainerd.

Station Hospital, Chico Army Air Base, California

April 19 Diagnosis of Deficiency Diseases—Dr. James F. Rinehart.
April 26 Newer Methods of Treatment of Heart Disease—Dr. Francis Chamberlain.

REGION No. 24 (Southern California)—Lt. Comdr. G. C. Griffith, Chairman; Capt. H. P. Schenck, Dr. W. A. Morrison, Dr. J. F. Churchill.

Station Hospital, U. S. Naval Air Training Station, San Diego, California

April 20 Treatment of Syphilis with Penicillin—Major Paul Recque.

A.A.F. Regional Hospital, Santa Ana, California

April 17 Surgery of the Traumatic Abdomen—Dr. Charles Phillips and Commander Gaylord Bates.

Station Hospital, March Field, Riverside, California

April 17 Blood Plasma and Blood Substitutes—Lieutenant Colonel R. M. Jones. Water Balance—Major Edward Schwartz.

ANNUAL FINANCIAL STATEMENT

THE AMERICAN COLLEGE OF PHYSICIANS, INC.

December 31, 1944

The following statements are taken from the report of the Auditor, December 31, 1944, and are published for the information of Fellows and Masters:

Balance Sheet

General Fund

Current Assets:			
Cash in Bank and on Hand		$ 39,618.80	
Accounts Receivable		2,669.09	
Inventory of Keys, Pledges and Frames		451.70	
Accrued Income on Investments		1,893.93	
Investments at Book Value		122,389.10	
Insurance Deposit		555.00	$167,577.62
Fixed Assets:			
Real Estate		$ 58,898.95	
Furniture and fixtures	$11,111.20		
Less Depreciation	8,691.08	2,420.12	61,319.07
TOTAL ASSETS, General Fund			$228,896.69
Liabilities:			
Current:			
Accounts Payable		$ 621.01	
Deferred Income:			
Advance Subscriptions, ANNALS OF INTERNAL MEDICINE		17,305.50	
Philadelphia Postgraduate Fund, Reserve		2,284.30	
TOTAL LIABILITIES, General Fund			$ 20,210.81
PRINCIPAL, General Fund			$208,685.88

Balance Sheet

Endowment Fund

Current Assets:		
Cash in Bank	$ 10,233.61	
Investments at Book Value	157,509.78	
Due from Brokers	2,000.00	
PRINCIPAL, Endowment Fund		$169,743.39
TOTAL PRINCIPAL, Both Funds		$378,429.27

	Jan. 1, 1944	*Dec. 31, 1944*	*Net Increase*
General Fund	$208,076.48	$208,685.88	$ 609.40
Endowment Fund	146,724.54	169,743.39	23,018.85
	$354,801.02	$378,429.27	$23,628.25

SUMMARY OF OPERATIONS

Year Ending December 31, 1944

General Fund

Income:		
Annual Dues		$ 23,100.56
Initiation Fees		5,350.50
Subscriptions, ANNALS OF INTERNAL MEDICINE		37,868.99
Advertising, ANNALS OF INTERNAL MEDICINE		13,279.83
Subscriptions, ANNALS OF CLINICAL MEDICINE		14.87
Income from Investments, Endowment Fund		5,362.50
Income from Investments, General Fund		5,604.43
Dividend on Perpetual Insurance Deposit		60.00
Sales of Miscellaneous Publications		6.43
Rent, Net, 404–12 S. 42nd Street		723.05
TOTAL, Income		$ 91,371.16
Expenditures:		
Salaries		$ 25,350.98
Postage, Telephone and Telegraph		3,891.36
Office Supplies and Stationery		1,241.36
Printing		25,741.36
Traveling Expenses, Executives, Committeemen, Regents		2,829.51
Miscellaneous		1,495.46
College Headquarters:		
Maintenance	$3,330.83	
Heat, Light, Gas and Water	779.76	
Taxes	170.77	
Insurance	85.05	4,366.41
Depreciation on Building	$1,000.00	
Depreciation on Furniture and Fixtures	833.04	1,833.04
Investment Counsel and Custodian Fees		472.18
Regional Meetings		2,574.83
1944 Postgraduate Courses		1,071.50
War-Time Graduate Medical Meetings		5,000.00
Collection and Exchange Fees		22.74
Loss on Sale or Maturity of Investments		970.81
1944 Supplement		330.02
Keys, Pledges and Frames		123.96
1944 Annual Meeting of Officers, Regents and Governors		7,395.41
TOTAL, Expenditures		$ 84,710.93
NET INCOME, Year Ending December 31, 1944		$ 6,660.23

General Fund Balance, January 1, 1944	$208,076.48	
Less: Transfer to Endowment Fund of Initiation Fees of New Life Members	6,035.00	
Transfer to Subscriptions, ANNALS OF INTERNAL MEDICINE	15.83	202,025.65
PRINCIPAL, General Fund		$208,685.88

Endowment Fund

Endowment Fund Balance, January 1, 1944	$146,724.54	
Add: Life Membership Fees Received During 1944	17,223.00	
Initiation Fees of New Life Members Transferred from General Fund	6,035.00	
Transfer of Dues of New Life Members	182.00	
Profit on Sale of Endowment Fund Investments	1.87	
	$170,166.41	
Less: Loss on Sale of Endowment Fund Investments	423.02	
PRINCIPAL, Endowment Fund		$169,743.39

OBITUARIES

DR. BERTNARD SMITH

The death occurred recently in Los Angeles of Dr. Bertnard Smith, F.A.C.P., for many years one of the outstanding members of the profession in that city.

Dr. Smith was born in Tyler, Texas in 1877, but spent most of his early life in Galesburg, Ill., graduating from Knox College in 1898. He received his degree in Medicine from Rush Medical College in 1903 and interned at the Presbyterian Hospital in Chicago, Illinois from 1904 to 1906. Later on he did Postgraduate Study at the University of Heidelberg, the University of Vienna and in 1914 at Harvard University, where he worked with Professor Otto Folin at the time that modern clinical methods applicable to chemical studies of the blood and urine were being developed. He served with the United States Army Medical Corps during World War I and during that time was closely associated with a group which had been organized for the study of cardiovascular disorders, especially neurocirculatory asthenia, being part of the time personally in charge of this investigation.

Dr. Smith had come West immediately following his internship and settled in Los Angeles. After he resumed his private practice in 1919 his chief interest became the care and treatment of diabetes. At a time when insulin still was expensive and difficult to obtain he was able, by soliciting private donations from friends, to supply a fairly large group of patients who were in serious need. Later he helped create the non-profit organization, Los Angeles Metabolic Clinic. He always was particularly concerned

in aiding the younger patients in mastering their problem and becoming self-supporting, and was for years a guiding influence of the Diabetic Service at Children's Hospital. He also organized the very fine Diabetic Clinic at the Cedars of Lebanon Hospital.

During his many years in Los Angeles he had become a member on the staffs of the Children's and Cedars of Lebanon Hospitals and a Life Member of the staff of the Hospital of the Good Samaritan. For a number of years he was Clinical Professor of Medicine at the University of Southern California School of Medicine. He was a member of the Los Angeles County Medical Association, the California Medical Association, the American Heart Association, the American Society for Clinical Investigation and a Fellow of the American College of Physicians.

Dr. Smith was a kindly, courteous man, wholly unselfish, seeking neither personal preferment nor financial gain. His place in the profession will not be easily filled and he leaves many close friends and faithful patients.

He is survived by his wife, Marion Macneil Smith, and one daughter, Mrs. Wilson Phelp.

Roy E. Thomas, M.D., F.A.C.P.
Governor for Southern California

DR. GEORGE ALLEN RICKETTS

Dr. George Allen Ricketts, F.A.C.P., Osceola Mills, Pa., died December 6, 1944, of cerebral embolism, at the age of seventy-one. Dr. Ricketts was born at Flinton, Pa., August 17, 1873. He held the degree of Master of Education from the Pennsylvania Central State Normal School. He graduated in medicine from Jefferson Medical College of Philadelphia in 1908, and did some postgraduate work at Harvard Medical School.

At one time he was a member of the staff of the Miners' Hospital, Spangler, Pa., and for many years Chief of the Medical Staff of the Philipsburg State Hospital.

Dr. Ricketts was a member and former President of the Clearfield County Medical Society, member of the Pennsylvania Medical Society and the American Medical Association; Fellow of the American College of Physicians since 1931. He retired from the practice of medicine in August, 1940, because of coronary thrombosis.